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(54) Title: PROTECTED FORMS OF PHARMACOLOGICALLY ACTIVE AGENTS AND USES THEREFOR

(57) Abstract: In accordance with the present invention, there are provided conjugates of dithiocarbamates ("DC") and pharmacologically active agents (e.g., NSAIDs). Invention conjugates provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein.

Protected Forms of Pharmacologically Active Agents and Uses Therefor

FIELD OF THE INVENTION

The present invention relates to novel conjugated forms of pharmacologically active agents, and methods for the preparation and use thereof. In a particular aspect of the invention, methods are provided for treating a pathological condition with a protected form of a pharmacologically active agent, thereby reducing the occurrence of side-effects caused thereby.

BACKGROUND OF THE INVENTION

Despite the advent of modern pharmaceutical technology, many drugs still possess untoward toxicities which often limit the therapeutic potential thereof. For example, although non-steroid anti-inflammatory drugs (NSAIDs) are a class of compounds which are widely used for the treatment of inflammation, pain and fever, NSAIDs (e.g., naproxen, aspirin, ibuprofen and ketoprofen) can cause gastrointestinal ulcers, a side-effect that remains the major limitation to the use of NSAIDs (see, for example, J. L. Wallace, in Gastroenterol. 112:1000-1016 (1997); A. H. Soll et al., in Ann Intern Med. 114:307-319 (1991); and J. Bjarnason et al., in Gastroenterol. 104:1832-1847 (1993)).

There are two major ulcerogenic effects of NSAIDs: (1) topical irritant effects on the epithelium of the gastrointestinal tract and (2) suppression of gastrointestinal prostaglandin synthesis. In recent years, numerous strategies have been attempted to design and develop new NSAIDs that reduce the damage to the gastrointestinal tract. These efforts, however, have largely been unsuccessful. For example, enteric coating or slow-release formulations designed to reduce the topical

irritant properties of NSAIDs have been shown to be ineffective in terms of reducing the incidence of clinically significant side effects, including perforation and bleeding (see, for example, D. Y. Graham et al., in Clin. Pharmacol. Ther. 38:65-70 (1985); and J. L. Carson, et al., in Arch. Intern. Med., 147:1054-1059 (1987)).

As another strategy to address the potential for NSAIDs to produce clinically significant side effects, Medford et al. (see, for example, PCT Publication No. WO 95/30415 and U.S. Patent No. 5,807,884) have proposed preparation of drug derivatives of dithiocarbomates having the structure:

A-S-C(S)-B,

wherein B represents the drug moiety. This specific structure is required because a goal of Medford's work is to maintain the accessability of the –C(S)-S- moiety as a reactive species.

It is well recognized that aspirin and other NSAIDs exert their pharmacological effects through the inhibition of cyclooxygenase (COX) enzymes, thereby blocking prostaglandin synthesis (see, for example, J. R. Van in Nature, 231:232-235 (1971)). There are two types of COX enzymes, namely COX-1 and COX-2. COX-1 is expressed constitutively in many tissues, including the stomach, kidney, and platelets, whereas COX-2 is expressed only at the site of inflammation (see, for example, S. Kargan et al. in Gastroenterol., 111:445-454 (1996)). The prostagladins derived from COX-1 are responsible for many of the physiological effects, including maintenance of gastric mucosal integrity.

Many attempts have been made to develop NSAIDs that only inhibit COX-2, without impacting the activity of COX-1 (see, for example, J.A. Mitchell et al., in Proc. Natl. Acad. Sci. USA 90:11693-11697 (1993); and E.A. Meade et al., in J. Biol. Chem., 268:6610-6614 (1993)). There are at least two NSAIDs presently on the market (i.e., nabumetone and etodolac) that show marked selectivity for COX-2 (see, for example, E. A. Meade, supra.; and K. Glaser et al., in Eur. J. Pharmacol. 281:107-111 (1995)). These drugs appear to have reduced gastrointestinal toxicity relative to other

NSAIDs on the market.

On the basis of encouraging clinical as well as experimental data, the development of highly selective COX-2 inhibitors appears to be a sound strategy to develop a new generation of anti-inflammatory drugs. However, the physiological functions of COX-1 and COX-2 are not always well defined. Thus, there is a possibility that prostagladins produced as a result of COX-1 expression may also contribute to inflammation, pain and fever. On the other hand, prostagladins produced by COX-2 have been shown to play important physiological functions, including the initiation and maintenance of labor and in the regulation of bone resorption (see, for example, D. M. Slater et al., in Am. J. Obstet. Gynecol., 172:77-82 (1995); and Y. Onoe et al., in J. Immunol. 156:758-764 (1996)), thus inhibition of this pathway may not always be beneficial. Considering these points, highly selective COX-2 inhibitors may produce additional side effects above and beyond those observed with standard NSAIDs, therefore such inhibitors may not be highly desirable.

Accordingly, there is still a need in the art for modified forms of NSAIDs, and other pharmacologically active agents, which cause a reduced incidence of side-effects, relative to the incidence of side-effects caused by such pharmacologically active agents as aspirin, ibuprofen, and the like.

BRIEF DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided conjugates of physiologically compatible dithiocarbamates (DC) and pharmacologically active agents (e.g., NSAIDs). Invention conjugates (e.g., DC-NSAIDs) provide a new class of pharmacologically active agents (e.g., anti-inflammatory agents) which cause a much lower incidence of side-effects due to the protective effects imparted by modifying the pharmacologically active agents as described herein.

There are a number of advantages of conjugates according to the

invention (e.g., DC-NSAID), including:

(i) reduced topical irritant effects of NSAIDs, and

(ii) enhanced tissue delivery of both drugs as a result of a decrease in net charges on the molecule, particularly for acidic NSAIDs such as naproxen, aspirin, diclofenac and ibuprofen, thereby reducing the quantity of material which must be delivered to achieve an effective dosage.

In accordance with the present invention, cleavage of the novel bio-cleavable conjugates described herein releases the active pharmaceutical agent. In contrast to the prior art, however (see, for example, Medford et al., referred to above), no free dithiocarbamate is released upon such cleavage. In the event the dithiocarbamate linkage is cleaved, a thiocarbonylcarboxy moiety (-C(S)-O-) will be generated instead of the dithiocarbonyl moiety (-C(S)-S-) required for a dithiocarbamate functionality. Thus, the means selected for linkage of a pharmacologically active agent to a dithiocarbamate has a dramatic effect on the species released *in situ*.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 illustrates the improved gastric safety of a Naproxen prodrug according to the invention (relative to unmodified Naproxen) in a rat model. The number of gastric lesions was measured three hours after oral dosing of fasted male Sprague-Dawley rats with vehicle, 2 different doses of naproxen or 2 different doses of a molar equivalent of Naproxen prodrug.

Figure 2 illustrates the alleviation of acute inflammation by Naproxen prodrug according to the invention in a carrageenen model in rats. Paw volume increases (measured with a Plethysmometer) are reported as a function of time, and were measured on the injected feet of male Sprague-Dawley rats which had been pretreated at –1 hour with oral vehicle, naproxen or Naproxen prodrug, then injected transdermally with 1% carrageenen. Blackened boxes represent untreated animals, checkered boxes represent animals to whom vehicle (5% DMSO/CMC) was

administered, open boxes represent naproxen administration at 3mg/kg, vertically lined boxes represent naproxen administration at 10 mg/kg, horizontally lined boxes represent Naproxen prodrug administration at 5.5 mg/kg (molar equivalent of 3 mg/kg naproxen alone), and diagonally cross-hatched boxes represent Naproxen prodrug /kg (molar equivalent of 10 mg/kg naproxen alone).

Figure 3 illustrates the effectiveness of Naproxen prodrug according to the invention in the treatment of adjuvant-induced arthritis in a rat model system. Thus, paw volume increases (measured with a Plethysmometer) are reported as a function of time, and were measured in the injected feet of Lewis male rats in which arthritis was induced by intradermal injection of adjuvant into the footpad. Rats were injected on day 0 and treated once orally with either vehicle, naproxen or Naproxen prodrug on days 5-8 and 11-14. Blackened boxes represent animals treated with vehicle (5% DMSO/CMC); checkered boxes represent animals treated with naproxen at 1 mg/kg, open boxes represent animals treated with naproxen at 10 mg/kg, vertically lined boxes represent animals treated with Naproxen prodrug at 1.8 mg/kg (molar equivalent of 1 mg/kg naproxen alone), and horizontally lined boxes represent animals treated with Naproxen prodrug, at 18 mg/kg (molar equivalent of 10 mg/kg naproxen alone).

Figure 4 presents concentration versus time curves for naproxen following IV administration of naproxen or Naproxen prodrug according to the invention. Blackened rectangles represent plasma concentration of naproxen following IV administration of 0.55 mg/kg of naproxen and open triangles represent plasma concentration of naproxen following IV administration of 1.1 mg/kg of Naproxen prodrug. After IV administration of naproxen, the naproxen plasma concentrations declined in a bi-exponential manner. The decline of plasma naproxen following Naproxen prodrug administration was monophonic. Note the lower plasma C_{max} shown for Naproxen prodrug.

Figure 5 presents concentration versus time curves for naproxen following oral administration of naproxen or Naproxen prodrug according to the invention. Open triangles represent plasma concentration of naproxen following oral administration of 2.2 mg/kg of naproxen and blackened rectangles represent plasma concentration of naproxen following oral administration of 4 mg/kg of Naproxen prodrug. Following oral administration of Naproxen prodrug, the time to maximum concentration of naproxen in plasma was considerably longer compared to naproxen administration (T_{max} of 6.4 and 1.3 hours for Naproxen prodrug and naproxen, respectively). The corresponding C_{max} values were 2.34 and 4.82 μg/mL for Naproxen prodrug and naproxen, respectively. There was no significant difference for AUC_{nif} values.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds comprising dithiocarbamate covalently attached to a pharmacologically active agent. Invention compounds comprise chemically modified pharmacologically active agents having the structure:

Z-C(S)-S-L-Q

wherein:

Q = a pharmacologically active agent,

L= a linker/spacer, and

Z = a modifying group.

Invention compounds can be readily prepared in a variety of ways, e.g., by reaction of dithiocarbamates with pharmacologically active agents employing a suitable linker/spacer.

Dithiocarbamates are sulfur-containing small molecules that are known heavy metal chelators (see, for example, F. W. Sunderman, in Ann. Clin. Lab. Sci., 8:259-69 (1978); and M. M. Jones and M. G. Cherian, in Toxicology, 62:1-25 (1990)). Dithiocarbamates such as diethyl-dithiocarbamate have been used clinically in the treatment of nickel poisoning (see, for example, Sunderman, supra) and were used in clinical trials for the treatment of AIDS patients (see, for example, E. Reisinger et al., in Lancet, 335:679 (1990)).

Dithiocarbamates such as pyrrolidine dithiocarbamate are potent inhibitors of nuclear factor kappa B in intact cells (see, for example, R. Schreck et al., in J. Exp. Med., 175:1181-1194 (1992)). In addition, nuclear factor kappa B has been shown to up-regulate the expression of cell adhesive molecules, including the vascular cell adhesive molecule 1 (VCAM-1; see, for example, M. F. Iademarco et al., in J. Biol. Chem., 267:16323-16329 (1992)). Endothelial expression of VCAM-1 causes the adherence of neutrophils to the endothelium, an early event leading to inflammation and subsequent vascular damage and reduction of blood flow (see, for example, M. N. Oppenheimer et al., in J. Immunol., 147:42207-4210 (1991)). It has been recognized that NSAID administration increases neutrophil adherence to the vascular endothelium in the gastric and mesenteric microcirculation (see, for example, J. L. Wallace et al., in Gastroenterol., 105:1630-1636 (1993); and H. Asako et al., in Am J. Physiol., 262:G903-G908 (1992)). Therefore, conjugates of NSAIDs with dithiocarbamate would block VCAM-1 expression, thereby avoiding the vascular problems associated with neutrophil adherence to the endothelium.

Suitable dithiocarbamate compounds contemplated for use in the practice of the present invention can be described with reference to generic structure **I** as follows:

$$[R_1R_2N\text{-}C(S)\text{-}S^-]_x\ M^{+1,+2,+3} \qquad (I)$$

wherein:

each of R_1 and R_2 is independently selected from a C_1 up to C_{18} alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, acyl, substituted acyl, or

R_1 and R_2 cooperate to form a 5-, 6- or 7-membered ring including N, R_1 and R_2, or

R_1 or R_2 is a divalent moiety selected from the group consisting of alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene and substituted aralkylene, wherein said divalent moiety serves as the same substituent for two dithiocarbamate structures, thereby linking said structures together so as to form a bis(dithiocarbamate) species,

x is 1 or 2, and

M is a monovalent cation when x is 1, or M is a physiologically compatible divalent or trivalent transition metal cation when x is 2.

Presently preferred dithiocarbamate compounds having generic structure I are those wherein:

each of R_1 and R_2 = a C_1 up to C_{12} alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl or substituted alkynyl, wherein the substituents are selected from carboxyl, -C(O)H, oxyacyl, phenol, phenoxy, pyridinyl,

pyrrolidinyl, amino, amido, hydroxy, nitro or sulfuryl, or

R_1 and R_2 cooperate to form a 5-, 6- or 7-membered ring including N, R_1 and R_2, and

$M = Na^+$ or NH^+_4.

Especially preferred dithiocarbamate compounds having generic structure **I** are those wherein:

R_1 is selected from a C_2 up to C_8 alkyl or substituted alkyl, wherein the substituents are selected from carboxyl, acetyl, pyridinyl, pyrrolidinyl, amino, amido, hydroxy or nitro, and

R_2 is selected from a C_1 up to C_6 alkyl or substituted alkyl, or

R_2 cooperates with R_1 to form a 5-, 6- or 7-membered ring including N, R_2 and R_1, and

$M = Na^+$ or NH^+_4.

The presently most preferred dithiocarbamate compounds having generic structure **I** are those wherein:

R_1 is selected from a C_2 up to C_8 alkyl or substituted alkyl, wherein the substituents are selected from carboxyl, acetyl, amido or hydroxy, and

R_2 is selected from a C_1 up to C_4 alkyl or substituted alkyl, or

R_2 cooperates with R_1 to form a 5- or 6-membered ring including N, R_2 and R_1, and

$M = Na^+$ or NH^+_4.

When R_1 and R_2 cooperate to form a 5-, 6- or 7-membered ring, the combination of R_1 and R_2 can be a variety of saturated or unsaturated 4, 5 or 6 atom bridging species selected from alkenylene or -O-, -S-,-C(0)- and/or -N(R)-containing alkylene moieties, wherein R is hydrogen or a lower alkyl moiety. Presently preferred dithiocarbamates wherein R_1 and R_2 cooperate to form a ring structure include

pyrrolidine dithiocarbamate, proline dithiocarbamate, pyridine dithiocarbamate, pyridinium dithiocarbamate, pyrimidine dithiocarbamate, pyrroline dithiocarbamate, and the like.

Examples of presently preferred dithiocarbamates contemplated for use herein for the preparation of invention conjugates include sarcosine dithiocarbamate, iminodiacetic acid dithiocarbamate, diethyldithiocarbamate, diisopropyldithiocarbamate, sugar-linked dithiocarbamates (e.g., glucose-, lactose-, mannose-, fructose-linked dithiocarbamates, and the like), pyrrolidine dithiocarbamate, proline dithiocarbamate, and the like.

Monovalent cations contemplated for incorporation into the above-described dithiocarbamate compounds include Na^+, NH_4^+, tetraalkyl ammonium, and the like. Physiologically compatible divalent or trivalent transition metal cations contemplated for incorporation into the above-described dithiocarbamate compounds include charged forms of iron, cobalt, copper, manganese, ruthenium, or the like (e.g., Fe^{+2}, Fe^{+3}, Co^{+2}, Co^{+3}, Cu^{+2}, Mn^{+2}, Mn^{+3} or Ru^{+3}). In accordance with the present invention, the ratio of dithiocarbamate-species to counter-ion M can vary widely. Thus, dithiocarbamate-containing nitric oxide scavenger can be administered without any added metallic counter-ion (i.e., M = H^+, or a transition metal cation to dithiocarbamate-species ratio of zero), with ratios of transition metal cation to dithiocarbamate-species up to about 1:2 (i.e., a 2:1 ratio of dithiocarbamate:transition metal cation) being suitable.

As employed herein, "substituted alkyl" comprises alkyl groups further bearing one or more substituents selected from hydroxy, alkoxy (of a lower alkyl group), mercapto (of a lower alkyl group), cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, aryl, substituted aryl, heteroaryl, substituted heteroaryl, aryloxy, substituted aryloxy, halogen, trifluoromethyl, cyano, nitro, nitrone, amino, amido, -C(O)H, acyl, oxyacyl, carboxyl, carbamate, sulfonyl, sulfonamide, sulfuryl, and the like.

As employed herein, "cycloalkyl" refers to cyclic ring-containing groups containing in the range of about 3 up to 8 carbon atoms, and "substituted cycloalkyl" refers to cycloalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkenyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon double bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkenyl" refers to alkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "alkynyl" refers to straight or branched chain hydrocarbyl groups having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms, and "substituted alkynyl" refers to alkynyl groups further bearing one or more substituents as set forth above.

As employed herein, "aryl" refers to aromatic groups having in the range of 6 up to 14 carbon atoms and "substituted aryl" refers to aryl groups further bearing one or more substituents as set forth above.

As employed herein, "alkylaryl" refers to alkyl-substituted aryl groups and "substituted alkylaryl" refers to alkylaryl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkyl" refers to aryl-substituted alkyl groups and "substituted arylalkyl" refers to arylalkyl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkenyl" refers to aryl-substituted alkenyl groups and "substituted arylalkenyl" refers to arylalkenyl groups further bearing one or more substituents as set forth above.

As employed herein, "arylalkynyl" refers to aryl-substituted alkynyl groups and "substituted arylalkynyl" refers to arylalkynyl groups further bearing one or more substituents as set forth above.

As employed herein, "aroyl" refers to aryl-carbonyl species such as benzoyl and "substituted aroyl" refers to aroyl groups further bearing one or more substituents as set forth above.

As employed herein, "heterocyclic" refers to cyclic (i.e., ring-containing) groups containing one or more heteroatoms (e.g., N, O, S, or the like) as part of the ring structure, and having in the range of 3 up to 14 carbon atoms and "substituted heterocyclic" refers to heterocyclic groups further bearing one or more substituents as set forth above.

As employed herein, "acyl" refers to alkyl-carbonyl species.

As employed herein, "halogen" refers to fluoride, chloride, bromide or iodide atoms.

Diseases and conditions contemplated for treatment in accordance with the present invention include inflammatory and infectious diseases, such as, for example, septic shock, hemorrhagic shock, anaphylactic shock, toxic shock syndrome, ischemia, cerebral ischemia, administration of cytokines, overexpression of cytokines, ulcers, inflammatory bowel disease (e.g., ulcerative colitis or Crohn□s disease), diabetes, arthritis, asthma, Alzheimer□s disease, Parkinson□s disease, multiple sclerosis, cirrhosis, allograft rejection, encephalomyelitis, meningitis, pancreatitis, peritonitis, vasculitis, lymphocytic choriomeningitis, glomerulonephritis, uveitis, ileitis, inflammation (e.g., liver inflammation, renal inflammation, and the like), burn, infection (including bacterial, viral, fungal and parasitic infections), hemodialysis, chronic fatigue syndrome, stroke, cancers (e.g., breast, melanoma, carcinoma, and the like),

cardiopulmonary bypass, ischemic/reperfusion injury, gastritis, adult respiratory distress syndrome, cachexia, myocarditis, autoimmune disorders, eczema, psoriasis, heart failure, heart disease, atherosclerosis, dermatitis, urticaria, systemic lupus erythematosus, AIDA, AIDS dementia, chronic neurodegenerative disease, chronic pain, priapism, cystic fibrosis, amyotrophic lateral sclerosis, schizophrenia, depression, premenstrual syndrome, anxiety, addiction, migraine, Huntington□s disease, epilepsy, neurodegenerative disorders, gastrointestinal motility disorders, obesity, hyperphagia, solid tumors (e.g., neuroblastoma), malaria, hematologic cancers, myelofibrosis, lung injury, graft-versus-host disease, head injury, CNS trauma, hepatitis, renal failure, liver disease (e.g., chronic hepatitis C), drug-induced lung injury (e.g., paraquat), myasthenia gravis (MG), ophthalmic diseases, post-angioplasty, restenosis, angina, coronary artery disease, and the like.

Pharmacologically active agents contemplated for modification in accordance with the present invention include:

NSAIDs, such as acetaminophen (Tylenol, Datril, etc.), aspirin, ibuprofen (Motrin, Advil, Rufen, others), choline magnesium salicylate (Triasate), choline salicylate (Anthropan), diclofenac (voltaren, cataflam), diflunisal (dolobid), etodolac (lodine), fenoprofen calcium (nalfon), flurobiprofen (ansaid), indomethacin (indocin, indometh, others), ketoprofen (orudis, oruvail), ketorolac tromethamine (toradol), magnesium salicylate (Doan□s, magan, mobidin, others), meclofenamate sodium (meclomen), mefenamic acid (relafan), oxaprozin (daypro), piroxicam (feldene), sodium salicylate, sulindac (clinoril), tolmetin (tolectin), meloxicam, nabumetone, naproxen, lornoxicam, nimesulide, indoprofen, remifenzone, salsalate, tiaprofenic acid, flosulide, and the like;

analgesics/antipyretics (e.g., aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine sulfate, oxycodone hydrochloride, codeine

phosphate, dihydrocodeine bitartrate, pentazocine hydrochloride, hydrocodone bitartrate, levorphanol tartrate, diflunisal, trolamine salicylate, nalbuphine hydrochloride, mefenamic acid, butorphanol tartrate, choline salicylate, butalbital, phenyltoloxamine citrate, diphenhydramine citrate, methotrimeprazine, cinnamedrine hydrochloride, meprobamate, and the like);

sedatives/hypnotics (e.g., barbiturates (e.g., pentobarbital, pentobarbital sodium, secobarbital sodium), benzodiazapines (e.g., flurazepam hydrochloride, triazolam, tomazeparm, midazolam hydrochloride, and the like);

antianginal agents (e.g., beta-adrenergic blockers, calcium channel blockers (e.g., nifedipine, diltiazem hydrochloride, and the like), nitrates (e.g., nitroglycerin, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, and the like));

antianxiety agents (e.g., lorazepam, buspirone hydrochloride, prazepam, chlordiazepoxide hydrochloride, oxazepam, clorazepate dipotassium, diazepam, hydroxyzine pamoate, hydroxyzine hydrochloride, alprazolam, droperidol, halazepam, chlormezanone, and the like);

antidepressants (e.g., doxepin hydrochloride, amoxapine, trazodone hydrochloride, amitriptyline hydrochloride, maprotiline hydrochloride, phenelzine sulfate, desipramine hydrochloride, nortriptyline hydrochloride, tranylcypromine sulfate, fluoxetine hydrochloride, doxepin hydrochloride, imipramine hydrochloride, imipramine pamoate, nortriptyline, amitriptyline hydrochloride, isocarboxazid, desipramine hydrochloride, trimipramine maleate, protriptyline hydrochloride, and the like);

antipsychotic agents (e.g., haloperidol, loxapine succinate, loxapine hydrochloride, thioridazine, thioridazine hydrochloride, thiothixene, fluphenazine hydrochloride, fluphenazine decanoate, fluphenazine enanthate, trifluoperazine hydrochloride, chlorpromazine hydrochloride, perphenazine, lithium citrate, prochlorperazine, and the like);

antimanic agents (e.g., lithium carbonate),

antiarrhythmics (e.g., bretylium tosylate, esmolol hydrochloride, verapamil hydrochloride, amiodarone, encainide hydrochloride, digoxin, digitoxin, mexiletine hydrochloride, disopyramide phosphate, procainamide hydrochloride, quinidine sulfate, quinidine gluconate, quinidine polygalacturonate, flecainide acetate, tocainide hydrochloride, lidocaine hydrochloride, and the like);

antihypertensive drugs, such as diuretics (hydrochlorothiazide, chlorthalidone, metolazone, indapamide, furosemide, bumetanide, torsemide, triamterene, amiloride, spronolactone), beta-adrenergic blocking agents (acebutolol, atenolol, betaxolol, cartelol, labetalol, metoprolol, nadolol, penbutolol, pindolol, propranolol, timolol), angiotensin converting enzyme inhibitors (benazepril, captopril, enalapril, fosinopril, quinoapril, ramimpril, losartan), calcium channel-blocking agents (diltiazem, verapamil, amlodipine, felodipine, isradipine, nicardipine, nifedipine), aplha-adrenoceptor blocking agents, sympatholytics, and vasodilators (such as prazosin, terazosin, doxazosin, clonidine, guanabenz, guanfacine, methylodopa, guanethidine, guanethidine monosulfate, reserpine, hydralazine, minoxidil, and the like), as well as agents such as trimethaphan camsylate, phenoxybenzamine hydrochloride, pargyline hydrochloride, deserpidine, diazoxide, rescinnamine, sodium nitroprusside, rauwolfia serpentina, alseroxylon, phentolamine mesylate, and the like;

antihistamine/antipruritic drugs, such as ethanolamines (e.g., diphenhydramine, diphenhydramine hydrochloride, clemastine, clemastine fumarate, and the like), ethylenediamines (e.g., brompheniramine, brompheniramine maleate, chlorpheniramine, chlorpheniramine maleate, dexchlorpheniramine maleate, triprolidine, triprolidine hydrochloride, and the like), phenothiazines (e.g., promethazine), piperidines (e.g., hydroxzine, hydroxyzine hydrochloride, terfenadine, astemizole, azatadine, azatadine maleate, and the like), cyproheptadine,

cyproheptadine hydrochloride, loratidine, carbinoxamine maleate, diphenylpyraline hydrochloride, phenindamine tartrate, tripelennamine hydrochloride, methdilazine hydrochloride, trimprazine tartrate, and the like;

immunosuppressants, such as glucocorticoids (methylprednisolone), myelin basic protein (e.g., 7-capaxone), anti-Fc receptor monoclonal antibodies, hydroorotate dehydrogenase inhibitor, anti-IL2 monoclonal antibodies (e.g., CHI-621 and dacliximab), buspirone, castanospermine, CD-59 (complement factor inhibitor), 5-lipoxygenase inhibitor (e.g., CMI-392), phosphatidic acid synthesis antagonists, ebselen, edelfosine, enlimomab, galaptin, platelet activating factor antagonists, selectin antagonists (e.g., ICAM-4), interleukin-10 agonist, macrocylic lactone, methoxatone, mizoribine, OX-19, peptigen agents, PG-27, protein kinase C inhibitors, phosphodiesterase IV inhibitor, single chain antigen binding proteins, complement factor inhibitor, sialophorin, sirolimus, spirocyclic lactams, 5-hydroxytryptamine antagonist, anti-TCR monoclonal antibodies, CD5 gelonin and TOK-8801, and the like;

antimetabolite cytotoxics (azathioprine, cyclophosphamide), C5a release inhibitor, benzydamine, peldesine, pentostatin, SDZ-ASM-981, thalidomide, benzoporphyrin derivatives, arachidonate antagonists (e.g., halometasone, halobetasol propionate), corticosteriod (clobetasol propionate), growth hormone antagonists (octapeptide somatostatin analogue, lanreotide, angiopeptin and dermopeptin), thymopentin, and the like;

neuroprotective agents, such as α-adrenoreceptor antagonist (i.e, α-dihydroergocryptine), NMDA antagonists (e.g., 5,6,7-tichloro-THQTQ, remacemide, 2-piperazinecarboxylic acid, N-indologlycinamide derivatives, spiro[benzo(b)thiophen-4(5H) derivatives, CP-101606, eliprodil, dexanabinol, GV-150526, L-695902, L-701324, amantadine derivatives, dizocilpine, benzomorphan derivatives, aptiganel, (S)-α-phenyl-2-pyridine ethanamide

dihyrochloride and 1-amino-cyclopentanecarboxylic acid), sodium channel antagonists (e.g., 619C89), glycine antagonists (e.g., glystasins), calcium channel antagonists (e.g., 3,5-pyridinedicarboxylic acid derivatives, conopeptides, 1-piperazineethanol, thieno[2,3-b]pyridine-5-carboxylic acid derivatives, NS-3034, nilvadipine, nisoldipine, tirilazad mesylate, 2H-1-enzopyran-6-ol, nitrone spin traps, iacidipine, iomeerzine hydrochloride, lemildipine, lifarizine, CPC-304, efonidipine, F-0401, piperazine derivatives), calpain inhibitors, fibrinogen antagonists (e.g., ancrod), integrin antagonists (e.g., antegren), thromboxane A_2 antagonist (e.g., 9H-carbazole-9-propanoic acid derivatives, 5-Heptenoic acid derivatives and 1-azulenesulfonic acid derivatives), brain-derived neurotropic factor, adrenergic transmitter uptake inhibitor (e.g., 1-butanamine), endothelin A receptor antagonists (e.g., benzenesulfonamide derivatives, GABA A receptor antagonists (e.g., triazolopyrimidine derivatives and cyclohexaneacetic acid derivatives), GPIIb IIIa receptor antagonists (e.g., C68-22), platelet aggregation antagonist (e.g., 2(1H)-quinolinone derivatives, 1H-pyrrole-1-acetic acid derivatives and coumadin), Factor Xa inhibitor, CPC-211, corticotropin releasing factor agonist, thrombin inhibitor (e.g., cothrombins, fraxiparine, dermatan sulfate and heparinoid), dotarizine, intracellular calcium chelators (e.g., BAPTA derivatives), radical formation antagonists (EPC-K1, 3-pyridinecarboxamide derivatives, superoxide dismutase, raxofelast, lubeluzole, 3H-pyrazol-3-one derivatives, kynurenic acid derivatives, homopiperazine derivatives, and polynitroxyl albumin), protein kinase inhibitors (e.g., 1H-1,4-diazepine), nerve growth agonist (e.g., floor plate factor-5), glutamate antagonist (e.g., cyclohexanepropanoic acid, riluzole, NS-409 and acetamide derivatives), lipid peroxidase inhibitor (e.g., 2,5-cyclohexadiene-1,4-dione derivatives), sigma receptor agonist (e.g., cyclopropanemethanamine derivatives and SA-4503), thyrotropin releasing hormone agonist (e.g., JTP-2942, L-prolinamide and

posatirelin), prolyl endopeptidase inhibitor, monosialoganglioside GM1, proteolytic enzyme inhibitor (e.g., nafamostat), neutrophil inhibitory factor, platelet activating factor antagonist (e.g., nupafant), monoamine oxidase B inhibitor (e.g., parafluoroselegiline and benzonitrile derivatives), PARS inhibitors, Angiotensin I converting enzyme inhibitor (e.g., perindopril and ramipril), acetylcholine agonist (e.g., pramiracetam), protein systhesis antagonist (e.g., procysteine), phosphodiesterase inhibitor (e.g., propentofylline), opioid kappa receptor agonist (e.g., 10H-phenothiazine-2-carboxamine derivatives), complement factor inhibitor (sCRI fragments), somatomedin-1, carnitine acetyltransferase stimulant (e.g., acetylcarnitine), and the like;

T cell inhibitors such as synthetic leucocyte antigen derived peptides, interleukin-1 receptor antagonist, MG/AnergiX, anti-CD3 monoclonal antibodies, anti-CD23 monoclonal antibodies, anti-CD28 antibodies, anti-CD2 monoclonal antibodies, CD4 antagonists, anti-E selectin antibodies, MHC inhibitors, monogens, mycophenolate mofetil, LRA-1 inhibitors, selectin inhibitors, and the like;

antimigraine agents, such as MK-462, 324C91, Phytomedicine, (S)-fluoxetine, calcium channel antagonists (e.g., nimodipine/Nimotop, flunarizine, dotarizine/FI-6026, iomerizine HCL/KB-2796, CPC-304, and CPC-317), α-dihydroergocryptine, 5-HT1 agonists, (e.g., Sumatriptan/Imitrex, Imigran, GR-85548, 311C, and GR-127607), 5-HT1D agonists, 5-HT1A antagonists, 5-HT1B antagonists (e.g., CP-93129), 5-HT1D antagonists (e.g., 1H-indole-5-ethanesulfonamide derivatvies and 1H-indole-5-methanesulfonamide), 5-HT1D receptor cloned (e.g., 5-HT1D agents), 2-thiophenecarboxamide, 3-piperidinamine, diclofenac potassium, dihydroergotamine (e.g., DHE 45®), ergotamine tartrate, dolasetron mesilate, dotarizine, flupirtine, histamine-H3 receptor agonist, indobufen, 1-azulenesulfonic acid derivatives, cholinesterase inhibitors, (e.g., S-9977), bradykinin antagonists, nitric oxide reductase inhibitors (e.g., BN-52296), nitric oxide receptor antagonists, substance P

antagonists (e.g., Capsaicin/Nasocap), endopeptidase inhibitors (e.g., neutral endopeptidase, cloned), piperazine derivatives, neurokinin 1 antagonists, metergoline, dopamine D2 antagonist (e.g., metoclopramide + lysine acetyl), enkephalinase inhibitors (e.g., neutral endopeptidase), 5-HT2 antagonists (e.g., LY-053857), 5-HT3 antagonists (e.g., Dolasetron mesilate/MDL-73147, and 4H-carbazol-4-one derivatives), tenosal, tolfenamic acid, cyclooxygenase inhibitors (e.g., carbasalate/carbaspirin calcium, and tenosal/MR-Y134), alpha adrenoreceptor antagonists (e.g., arotinolol, and dihydroergocryptine), opioid agonists (e.g., flupirtine/D-9998), beta adrenergic antagonists (e.g., propranolol), valproate semisodium, propanolol hydrochloride, isometheptene mucate, dichloralphenazone, and the like;

antiarthritic agents, such as anti-CD4 monoclonal antibodies, phospholipase A1 inhibitor, loteprednol, tobramycin, combinations of loteprednol and tobramycin, salnacedin, amiprilose, anakinra, anergiX, anti-B7 antibody, anti-CD3H, anti-gp39, anti-MHC MAbs, antirheumatic peptides, anti-Tac(Fv)-PE40, AP-1 inhibitors, AR-324, purine nucleotide phosphorylase inhibitors (e.g., BCX-5), bindarit, CD2 antagonist (e.g., BTI-322), campath-1H, CD4 antagonist (e.g., CE9.1 and SB-210396), tumor necrosis factor antagonist (e.g., p80 TNFR, rhTNFbp, peptide T, CenTNF, thalidomide, CDP-571 and TBP-1), cobra venom factor, interleukin 1a agonist (e.g., cytogenin), interleukin 2 receptor antagonist (e.g., dacliximab), ICAM 1 antagonist (e.g., enlimomab), interleukin 1 beta converting enzyme inhibitors (e.g., ICE-inhibitors), interferons (e.g., thymocartin), interleukin-10, interleukin-13, interleukin 1 antagonist (e.g., SR-31747 and TJ-114), interleukin-2 antagonist (e.g., sirolimus), phospholipase C inhibitor, neurokinin 1 antagonist (e.g., L-733060), laflunimus, leflunomide, leucotriene antagonists, levamisole, LFA3TIP, macrocyclic lactone, MHC class II inhibitors, mizoribine, mycophenolate mofetil, NfκB inhibitors, oncolysin CD6, peldesine, pidotimod, PKC-RACK inhibitors, PNP inhibitors, reumacon, CD28

antagonist, roquinimex, RWJ-50271, subreum, T7 vector, tacrolimus, VLA antagonist (e.g., TBC-772), transforming growth factor beta agonist, methionine synthase inhibitors (e.g., vitamin B12 antagonist), adenosine A2 receptor agonist (e.g., YT-146), CD5 antagonist (e.g., zolimomab), 5-lipoxygenase inhibitor (e.g., zileuton, tenidap, and ABT-761), cyclooxygenase inhibitor (e.g., tenoxicam, talmetacin, piroxicam, piroxicam cinnamate, oxaprozin, NXTHIO, ML-3000, mofezolac, nabumetone, flurbiprofen, aceclofenac, diclofenac, and dexibuprofen), metalloproteinase inhibitor (e.g., XR-168, TNF convertase inhibitors, GI-155704A, AG-3340 and BB-2983), nitric oxide synthase inhbitors (i.e, ARL-16556), phospholipase A2 inhibitor (e.g., ARL-67974), selectin antagonist (e.g., CAM inhibitors), leucotriene B4 antagonist (e.g., CGS-25019C), collagenase inhibitor (e.g., GR-129574A), cyclooxygenase 2 inhibitor (e.g., meloxicam), thromboxane synthase inhibitor (e.g., curcumin), cysteine protease inhibitor (e.g., GR-373), metalloproteinase inhibitor (D-5410), lipocortins synthesis agonist (e.g., rimexolone, predonisolone 21-farnesylate, HYC-141, and deflazacort), chelating agent (diacerein), elastase inhibitors, DNA directed RNA polymerase inhibitor (e.g., estrogens), oxygen radical formation antagonist (e.g., glucosamine sulfate), thrombin inhibitors (e.g., GS-522), collagen inhibitors (e.g., halofuguinone), hyaluronic acid agonist (e.g., NRD-101, hylan, Dispasan, and Hyalart), nitric oxide antagonists (e.g., hydroxocobalamin), stromelysin inhibitors (e.g., L-758354), prostaglandin E1 agonist (e.g., misoprostol, and misoprostol+diclofenac), dihydrofolate reductase inhibitor (e.g., trimetrexate, and MX-68), opioid antagonist (e.g., nalmefene), corticotropin releasing factor antagonist (e.g., NBI-103, and NBI-104), proteolytic enzyme inhibitor (e.g., protease nexin-1, and NCY-2010), bradykinin antagonist (e.g., tachykinin antagonists, and NPC-17731), growth hormone antagonist (e.g., octreotide), phosphodiesterase IV

inhibitor (e.g., PDEIV inhibitors), gelatinase inhibitor (e.g., REGA-3G12), free radical scavengers (e.g., SIDR-1026), prostaglandin synthase inhibitors (e.g., sulfasalazine), phenylbutazone, penicillamine, salsalate, azathioprine, indomethacin, meclofenamate sodium, gold sodium thiomalate, ketoprofen, auranofin, aurothioglucose, tolmetin sodium, and the like;

antigout agents (e.g., colchicine, allopurinol, and the like);

anticoagulants (e.g., heparin, heparin sodium, warfarin sodium, and the like);

thrombolytic agents (e.g., urokinase, streptokinase, altoplase, and the like);

antifibrinolytic agents (e.g., aminocaproic acid);

hemorheologic agents (e.g., pentoxifylline);

antiplatelet agents (e.g., aspirin, empirin, ascriptin, and the like);

anticonvulsants (e.g., valproic acid, divalproate sodium, phenytoin, phenytoin sodium, clonazepam, primidone, phenobarbitol, phenobarbitol sodium, carbamazepine, amobarbital sodium, methsuximide, metharbital, mephobarbital, mephenytoin, phensuximide, paramethadione, ethotoin, phenacemide, secobarbitol sodium, clorazepate dipotassium, trimethadione, and the like);

agents useful for calcium regulation (e.g., calcitonin, parathyroid hormone, and the like);

antibacterial agents (e.g., amikacin sulfate, aztreonam, chloramphenicol, chloramphenicol palmitate, chloramphenicol sodium succinate, ciprofloxacin hydrochloride, clindamycin hydrochloride, clindamycin palmitate, clindamycin phosphate, metronidazole, metronidazole hydrochloride, gentamicin sulfate, lincomycin hydrochloride, tobramycin sulfate, vancomycin hydrochloride, polymyxin B sulfate, colistimethate sodium, colistin sulfate, and the like);

antifungal agents (e.g., griseofulvin, keloconazole, and the like);

antiviral agents (e.g., interferon gamma, zidovudine, amantadine hydrochloride, ribavirin, acyclovir, and the like);

antimicrobials (e.g., cephalosporins (e.g., cefazolin sodium, cephradine, cefaclor, cephapirin sodium, ceftizoxime sodium, cefoperazone sodium, cefotetan disodium, cefutoxime azotil, cefotaxime sodium, cefadroxil monohydrate, ceftazidime, cephalexin, cephalothin sodium, cephalexin hydrochloride monohydrate, cefamandole nafate, cefoxitin sodium, cefonicid sodium, ceforanide, ceftriaxone sodium, ceftazidime, cefadroxil, cephradine, cefuroxime sodium, and the like), penicillins (e.g., ampicillin, amoxicillin, penicillin G benzathine, cyclacillin, ampicillin sodium, penicillin G potassium, penicillin V potassium, piperacillin sodium, oxacillin sodium, bacampicillin hydrochloride, cloxacillin sodium, ticarcillin disodium, azlocillin sodium, carbenicillin indanyl sodium, penicillin G potassium, penicillin G procaine, methicillin sodium, nafcillin sodium, and the like), erythromycins (e.g., erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin siearate, erythromycin ethylsuccinate, and the like), tetracyclines (e.g., tetracycline hydrochloride, doxycycline hyclate, minocycline hydrochloride, and the like), and the like);

antioxidants (e.g., N-acetylcsysteine, Vitamin A, Vitamin C, Vitamin E, β carotene, EUK-8, flavonoids, glutathione, α-lipoic acid, melatonin, retinols, and the like);

anti-infectives (e.g., miconazole, vidarabine, inosine, pranobex, vidarabine, inosine prabonex, cefpimizole sodium), fradiomycin, and the like);

bronchodialators (e.g., sympathomimetics (e.g., epinephrine hydrochloride, metaproterenol sulfate, terbutaline sulfate, isoetharine, isoetharine mesylate, isoetharine hydrochloride, albuterol sulfate, albuterol, bitolterol, mesylate isoproterenol hydrochloride, terbutaline sulfate, epinephrine bitartrate, metaproterenol sulfate, epinephrine, epinephrine bitartrate), anticholinergic agents (e.g., ipratropium bromide), xanthines (e.g., aminophylline, dyphylline, metaproterenol sulfate, aminophylline),

mast cell stabilizers (e.g., cromolyn sodium), inhalant corticosteroids (e.g., flurisolidebeclomethasone dipropionate, beclomethasone dipropionate monohydrate), salbutamol, beclomethasone dipropionate (BDP), ipratropium bromide, budesonide, ketotifen, salmeterol, xinafoate, terbutaline sulfate, triamcinolone, theophylline, nedocromil sodium, metaproterenol sulfate, albuterol, flunisolide, and the like);

hormones (e.g., androgens (e.g., danazol, testosterone cypionate, fluoxymesterone, ethyltostosterone, testosterone enanihate, methyltestosterone, fluoxymesterone, testosterone cypionate), estrogens (e.g., estradiol, estropipate, conjugated estrogens), progestins (e.g., methoxyprogesterone acetate, norethindrone acetate), corticosteroids (e.g., triamcinolone, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate, prednisone, methylprednisolone acetate suspension, triamcinolone acetonide, methylprednisolone, prednisolone sodium phosphate methylprednisolone sodium succinate, hydrocortisone sodium succinate, methylprednisolone sodium succinate, triamcinolone hexacatonide, hydrocortisone, hydrocortisone cypionate, prednisolone, fluorocortisone acetate, paramethasone acetate, prednisolone tebulate, prednisolone acetate, prednisolone sodium phosphate, hydrocortisone sodium succinate, and the like), thyroid hormones (e.g., levothyroxine sodium) and the like), and the like;

hypoglycemic agents (e.g., human insulin, purified beef insulin, purified pork insulin, glyburide, chlorpropamide, glipizide, tolbutamide, tolazamide, and the like);

hypolipidemic agents (e.g., clofibrate, dextrothyroxine sodium, probucol, lovastatin, niacin, and the like);

proteins (e.g., DNase, alginase, superoxide dismutase, lipase, and the like);

nucleic acids (e.g., sense or anti-sense nucleic acids encoding any therapeutically active protein, including the proteins described herein, and the like);

agents useful for erythropoiesis stimulation (e.g., erythropoietin);

antiulcer/antireflux agents (e.g., famotidine, cimetidine, ranitidine hydrochloride, and the like);

antinauseants/antiemetics (e.g., meclizine hydrochloride, nabilone, prochlorperazine, dimenhydrinate, promethazine hydrochloride, thiethylperazine, scopolamine, and the like);

septic shock agents, such as angiogenesis inhibitors (OLX-514), bradykinin antagonists (e.g., CP-0502, and NPC-17731), complement factor inhibitors (e.g., C3 convertase inhibitor), C5a release inhibitors (e.g., CAB-2.1), dopamine agonists (e.g., dopexamine), elastase inhibitors (e.g., ONO-5046), E selectin antagonists (e.g., CY-1787), farnesyltransferase inhibitors (RBE limonene), immunostimulants (e.g., CGP-19835A, lipid A vaccine, edobacomab, nebacumab, StaphGAM, and diabodies), immunosuppressants (e.g., CytoTAB, and transcyclopentanyl purine analogues), interleukin 1 antagonists (e.g., interleukin 1 receptors), interleukin 1 receptor antagonists (e.g., anakinra), interleukin 1b antagonists (e.g., interleukin-1β), interleukin 1beta converting enzyme inhibitors (e.g., ICE-inhibitors), interleukin 8 antagonists (e.g., IL-8 receptor), interleukin 13 agonists (e.g., intereleukin-13), ITF-1697, lipase clearing factor inhibitors (e.g., SC-59735), membrane permeability enhancers (e.g., Bactericidal Permeability Increasing protein/BPI), nitric oxide antagonists (e.g., hydroxocobalamin), nitric oxide synthase inhibitors (e.g., L-NMMA, and α-methyl-N-delta-iminoethyl-ornithine), P2 receptor stimulants (e.g., ATP analogues), phosphatidic acid synthesis antagonists (e.g., lisofylline), phospholipase A2 inhibitors (e.g., S-448, acylpyrrole-alkanoic acid derivatives, and indoleacetic acid derivatives), platelet activating factor antagonists (e.g., ABT-299, TCV-309, SM-12502, (2RS,4R)-3-(2-(3-pyridinyl)-thiazolidin-4-oyl)indoles, UR-12670, and E-5880), prostacyclin agonists (e.g., taprostene), prostaglandin E1 agonists (e.g., TLC C-53), protein

kinase inhibitors (e.g., SB-203580), protein kinase C inhibitors, protein synthesis antagonists (e.g., procysteine), proteolytic enzyme inhibitors (e.g., nafamostat), SDZ-PMX-622, selectin antagonists (e.g., sulfated glycolipid cell adhesion inhibitors), thrombin inhibitors (e.g., GS-522), TNF receptor-Ig, tumor necrosis factor antagonists (e.g., anti-TNF MAbs, MAK-195F, TBP-I, Yeda, rhTNFbp, and CDP-571), tumor necrosis factor alpha antagonists (e.g., E-5531), and the like;

multiple sclerosis agents, such as 4-aminopyridine, 15-deoxyspergualin, ACTH, amantadine, antibody adjuvants (e.g., poly-ICLC, and poly-IC+poly-L-lysine+carboxymethylcellulose), anti-cytokine MAb (CDP-835), anti-inflammatory (e.g., CY-1787, and CY-1503), anti-selectin MAb (e.g., CY-1787), anti-TCR MAb (e.g., NBI-114, NBI-115, and NBI-116), bacloten, bethanechol chloride, carbamazepine, carbohydrate drugs (e.g., CY-1503), clonazepam, CNS and immune system function modulators (e.g., NBI-106, and NBI-107), cyclophosphamide, cyclosporine A, cytokines (e.g., IFN-α, lfaferone, IFN-β 1b, betaseron, TGF-β2, PEG-TGF-β2, betakine, IFN- β/Rebif, frone, interferon-β, and IFN-β), CD4+T cell inhibitors (e.g., AnergiX), CD28 antagonists (e.g., B7-1, B7-2, and CD28), directcytotoxicity therapies (e.g., benzoporphyrin derivative (BPD)), FK-506, growth factors (e.g., glial growth factor, GGF, nerve growth factors, TGF-β2, PEG-TGF-β2, and betakine), humanized MAb (e.g., anti-IFN-γMAb, smart anti-IFN-γMAb, anti-Tac antibody, and smart anti-Tac antibody), humanized anti-CD4 MAb (e.g., anti-CD4 MAb, centara), hydrolase stimulants (e.g., castanospermine), IFN-α, IFN-γ antagonist (e.g., anti-IFN-γ MAb, and smart anti-IFN-γ MAb), IL-2 antagonists (e.g., tacrolimus, FK-506, FR-900506, Fujimycin, Prograf, IL-2 fusion toxin, and DAB_{389}IL-2), IL-4 antagonists (e.g., IL-4 fusion toxin, and DAB_{389}IL-4), immune-mediated neuronal damage inhibitors (e.g., NBI-114, NBI-115, and NBI-116), immunoglobins, immunostimulants (e.g., poly-ICLC, edelfosine, ALP, ET-18-OCH3, ET-18-OME,

NSC-24, and poly-IC+poly-L-lysine+carboxymethyl-cellulose), immunosuppressants (e.g., azathioprine, AI-100 animal protein, rDNA human protein AI-101, peptide, AI-102, castanospermine, tacrolimus, FK-506, FR-900506, Fujimycin, Prograf, anti-leukointegrin MAb, Hu23F2G, primatized anti-CD4 antibody, CE9.1, Galaptin 14-1, GL14-1, Lectin-1, recombinant IML-1, linomide, roquinimex, LS-2616, transcyclo-pentanyl purine analogs, MS-6044, spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCL, NSC-356894, NKT-01, TCR, CD3/Ti, cyclosporine, OL-27-400, SandImmune, Human IL-10, monogens, anti-TCR MAbs, TCAR MAbs, Monogen TM19, Monogen TM27, Monogen TM29, Monogen TM31, peptigen TP12, anti-CD4 MAb, cantara, immunophilins, VX-10367, VX-10393, VX-10428, synthetic basic copolymer of amino acids, copolymer-1, COP-1, T lymphocyte immunofusion (TIF) protein, and cyclophosphamide), integrin antagonists (e.g., anti-integrin (cell adhesion molecule $\alpha 4\beta 1$ integrin) MAbs, AN-100225, and AN-100226), interferon agonists (e.g., poly-ICLC, and poly-IC+poly-L-lysine+carboxymethyl-cellulose), interferon-β-1b, isoprinosine, IV methylprednisolone, macrolides (e.g., tacrolimus, FK-506, FR-900506, Fujimycin, and Prograf), MAO B inhibitors (e.g., selegiline, and Parkinyl), methotrexate, mitoxantrone, muscle relaxants (e.g., RGH-5002), muscarinic antagonists (e.g., RGH-5002), neurosteroids (e.g., NBI-106, and NBI-107), octapeptides (e.g., peptide T), oxybutinin chloride, oxygen free radical antagonists (e.g., tetrandrine, biobenzylisoquinoline alkaloid), peptide agonists (e.g., peptide T), phenoxybenzamine, phospholipase C inhibitors (e.g., edelfosine, ALP, ET-18-OCH3, ET-18-OME, NSC-24), photodynamic therapies (e.g., benzoporphyrin derivative (BPD)), plasmapheresis, platelet activating factor antagonists (e.g., ginkgolide B, and BN-52021), potassium channel antagonists (e.g., aminodiaquine, and EL-970), propranolol, prostaglandin synthase inhibitors (e.g., sulfasalazine,

salazosulfa-pyridine, PJ-306, SI-88, azulfidine, salazopyrin), protease antagonists (e.g., ginkgolide B, and BN-52021), recombinant soluble IL-1 receptors, spergualin analogs (e.g., spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus HCl, NSC-356894, NKT-01), TCR peptide decoys (e.g., NBI-114, NBI-115, and NBI-116), TCR peptidomimetic decoys (e.g., NBI-114, NBI-115, and NBI-116), TCR peptide vaccines (e.g., AI-208 (Vβ6.2/6.5 phenotype)), selectin antagonists (e.g., lectin-1, and recombinant IML-1), soluble TNF receptor I, TCARs (e.g., TCR, CD3/Ti, and peptigen TP12), TNF antagonists (e.g., thalidomide, and TNF inhibitors), tricyclic antidepressants, and the like;

organ transplantation agents, such as anti-CD25 MAbs, anti-Tac antibodies, anti-TNF MAb (e.g., CDP571), apoptosin, azathioprines (e.g., imuran), BCX-34, CA3, CD28, complement inhibiting factors (e.g., CD59), CTLA4Ig, cyclosporines (e.g., CsA), FK-506/rapamycin binding proteins (FKBP), glucocorticoids, humanized version of OKT3 (e.g., huOKT3-185), mycophenolate mofetil, hydroorotate dehydrogenase inhibitors (e.g., Brequinar), orthoclone OKT3 (e.g., IgG2a anti-T cell murine monoclonal antibody, and muromonab-CD3), rapamycins (e.g., AY-22989), and streptomyces isolates (e.g., FR-900520, and FR-900523), and the like;

systemic lupus erythematosus (SLE) agents, such as androgen-derived steriods (e.g., Org-4094), anti-CD4 humanized antibodies, anti-DNA/V-88, anti-idiotypic murine MAb (e.g., anti-idiotypic antibody to 3E10/MAb1C7), CD2 antagonists (e.g., CD2), complement inhibitors (e.g., recombinant MCP-based complement inhibitors), cyclosporines (e.g., Sandimmune, cyclosporine analog, OG-37325, cyclosporin-G, and NVal-CyA), cytokines (e.g., IL-4 fusion toxin), cytokine receptor antagonists (e.g., immunomodulatory cytokines), E-selectin antagonists (e.g., anti-ELAM, and CY-1787), FK506/tacrolimus (e.g., Prograf), hypercalcemic agents (e.g., KH-1060), IFN-γ antagonists (e.g., anti-IFN-γ MAb, and smart anti-IFN-γ MAb), IL-1β converting enzyme

inhibitors (ICE), IL-2 produced by *E. coli* (e.g., celmoleukin, IL-2, TGP-3, and Celeuk), immunoglobulins (e.g., anti-ELAM, CY-1788, and humanized CY-1787), immunostimulants (e.g., thymotrinan, RGH-0205, and TP3), immunosuppressants (e.g., Rapamycin, AY-22989, NSC-226080, NSC-606698, anti-CD4, T-cell inhibitor, anti-tac MAb, smart anti-tac MAb, Migis (membrane immunoglobulin-isotope specific) antibodies, SM-8849, immunophilins, VX-10367, VX-10393, VX-10428, mycophenolate mofetil, ME-MPA, RS-61444, cyclosporine, OL-27-400, Sandimmune, IL-4 fusion toxin, trypanosomal inhibitory factor (TIF), T-cell receptor, CD3/Ti, Org-4094, anti-TBM, CP 17193, Leflunomide/A-77-1726, ELAM-1, AnergiX, Spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus hydrochloride, NSC-356894, NKT-01, Roquinimex, LS-2616, linomide, LJP-394, and CD-59 antigen), immunotoxins (e.g., Zolimomab aritox, xmmly-h65-rta, xomazyme-lym/CD5-Plus, OrthoZyme-CD5+, XomaZyme-H65-rta, Xomazyme-CD5 Plus), intravenous immunoglobulins (e.g., IVIG), integrin antagonists (e.g., integrin blockers), Migis□ antibodies, monoclonal antibody therapeutics, murine MAb (e.g., anti-SLE vaccine, and MAb 3E10), primatized anti-CD4 antibodies (e.g., CE9.1), protease inhibitors (e.g., matrix metalloprotease (MMP) inhibitors, and stromelysin), protein synthesis antagonists (e.g., anti-CD6-bR, anti-T12-bR, and oncolysin CD6), purine nucleoside phosphorylase inhibitors (e.g., BCX-25, and BCX-14), selectin antagonists (e.g., CY1503, and Cylexin), spergualin analogues (e.g., Spanidin, 15-deoxyspergualin, deoxyspurgiline, gusperimus hydrochloride, NSC-356894, and NKT-01), T cell inhibitors (e.g., AnergiX), tumor necrosis factor (TNF) antagonists, and the like;

Alzheimer's disease agents, such as ACh release enhancers (e.g., T-588 (benzothiophene derivative)), acetylcholine release stimulants (e.g., DUP-996 and analogues), AMPA agonists (e.g., AMAlex, and Isoxazole compound series), AMPA GluR agonist (e.g., IDRA-21 [7-chloro-3-methyl-3,4-dihydro-2H-1,2,4-benzothiadiazinine]), AMPA GluR antagonists (e.g., S-18986, and related quinolone derivatives), anticholinesterases (e.g., E-2020), Ca-antagonists (e.g., NS-649, spider venom-derived ICM peptides and analogues, and substituted 2-aminoindanes compound series), combined anticholinesterase and muscarinic AChR antagonists (e.g., PD142676), K-channel blockers (e.g., Trans-R-4-(4-methoxyphenyl-methyl) cyclohexylanine and analogues, and margatoxin-based functional and/or structural analogues), MI muscarinic receptor agonists (e.g., Xanomeline), NMDA antagonists (e.g., certain indole derivatives, and (R-(R^1,S^1))-α-(4-hydroxyphenyl)-beta-methyl-4-(phenylmenthyl)-1-piperidinepropanol and analogues), nicotinic AChR agonists (e.g., ABT-418 [isoxazole, 3-meth-5-(1-meth-2-pyrrolidinyl)]), and the like;

antiparkinson agents (e.g., ethosuximide, and the like);

psoriasis agents, such as 5-LO inhibitors (e.g., Wy-50295, Wy-49232, Lonapalene, RS-43179, MK-886, L-663536, ETH-615, DUP-654, Zileuton, epocarbazolin-A, and A-64077), 5-LO/CO inhibitors (e.g., BF-397, Tenidap, CP-309, and CP-66248), angiogenesis inhibitors (e.g., platelet factor 4), anticancer antibiotic (e.g., AGM-1470, and TNP-470), anti-inflammatory cytochrome P450 oxidoreductase inhibitors (e.g., DuP-630, and DuP-983), antiproliferative compounds (e.g., Zyn-Linker), arachidonic acid analogues (e.g., CD581, and CD554), arachidonic acid antagonists (e.g., Lonopalene, RS-43179, triamcinolone acetonide with penetration enhancer Azone, betamethasone dipropionate steroid wipe, G-202, Halobetasol propionate, ultravate, Halometasone, C-48401-Ba, and Sicorten), beta-glucan receptor antagonists, betamethasone steroid

wipes, calcium metabolic moderators (e.g., Tacalcitol, Bonealfa, TV-02 ointment, Ro-23-6474, KH-1060, Calcipotriol, BMS-181161, BMY-30434, Dovonex, and Divonex), CD4 binding inhibitors (e.g., PIC 060), cell adhesion compounds (e.g., CY-726, VCAM-1, ELAM-1, and ICAM), cell adhesion inhibitors (e.g., selectin inhibitor, GM-1930), cellular aging inhibitors (e.g., Factor X), corticosteroids (e.g., Halobetasol propionate, ultravate, Halometasone, C-48401-Ba, and Sicorten), cyclosporin analogues (e.g., IMM-125), dihydrofolate reductase inhibitors (e.g., G-301, dichlorobenzoprim, methotrexate, and methotrexate in microsponge delivery system), E-selectin inhibitors (e.g., ISIS 4730), endogenous active form of vitamin D_3 (e.g., Calcitriol, and Du- 026325), fibroblast growth factor antagonists (e.g., Saporin mitotoxin, and Steno-Stat), fumagillin analogues (e.g., AGM-1470, and TNP-470), G-proteins and signal transduction compounds (e.g., CPC-A), gel formulations for acne (e.g., nicotinamide, N-547, and Papulex), growth hormone antagonists (e.g., Octreotide, Sandostatin, Lanreotide, angiopeptin, BIM-23014, and Somatuline), humanized antibodies (e.g., anti-CD4 antibody), hydroorotate dehydrogenase inhibitors (e.g., Brequinar sodium, bipenquinate, and DuP-785), ICAM-1 inhibitors (e.g., ISIS 939), IL-1 and other cytokine inhibitors (e.g., Septanil), IL-1 converting ezyme inhibitors, IL-1 receptor antagonists (e.g., Antril), IL-2 antagonists (e.g., Tacrolimus, Prograf, and FK-506), IL-2 receptor-targeted fusion toxins (DAB389IL-2), IL-8 receptors, immunostimulants (e.g., Thymopentin, and Timunox), immunosuppressants (e.g., XomaZyme-CD5 Plus, cyclosporine, Sandimmune, SR-31747, anti-CD11, 18 MAb, Tacrolimus, Prograf, FK-506, and FK-507), immunosuppressive agents targeting FK506 (e.g., immunophilins, VX-10367, and VX-10428), immunotoxins MAb directed against CD antigen (e.g., XomaZyme-CD5 Plus), leukotriene antagonists (e.g., Sch-40120, Wy-50295, and Wy-49232), leukotriene B4 antagonists (e.g., SC-41930, SC-50605, SC-48928, ONO-4057,

LB-457, LY-255283, LY-177455, LY-223982, LY-223980, and LY-255253), leukotriene synthesis inhibitors (MK-886, and L-663536), lipase clearing factor inhibitors (e.g., 1-docosanol, and lidakol), lipid encapsulated reducing agent (e.g., Dithranol), liposomal gel (e.g., Dithranol), LO inhibitors (e.g., CD581, CD554, Masoprocol, and Actinex), lithium succinate ointments (e.g., lithium salts, and Efalith), LO/CO inhibitors (e.g., P-8892, P-8977, CHX-108, and FPL-62064), membrane integrity agonists (e.g., lithium salts, and Efalith), microtubule inhibitors (e.g., Posophyliotoxin-containing compound, and Psorex), octapeptide somatostatin analogues (e.g., Lanreotide, angiopeptin, BIM-23014, and Somatuline), oligonucleotides (e.g., ISIS 4730, ISIS 3801, ISIS 1939, and IL-1 inhibitors), peptide agonists (e.g., octapeptide, and peptide T), PKC inhibitors, phospholipase A2 compounds, pospholipase D compounds, photodynamic anticancer agents (e.g., 5-aminolevulinic acid, and 5-ALA), photodynamic therapies (e.g., benzoporphyrin derivative, synthetic chlorins, synthetic porphyrins, and EF-9), photosensitizer (e.g., Porfirmer sodium), PKC inhibitors (e.g., Safingol, and Kynac), platelet activating factor antagonists (e.g., TCV-309), platelet aggregation inhibitors (e.g., CPC-A), prodrug NSAIDs (e.g., G-201), prostaglandin agonist (e.g., eicosapentaenoic acid + gamma-linolenic acid combination, and Efamol Marine), protein inhibitors (e.g., SPC-103600, and SPC-101210), protein kinase C (PKC) inhibitors (e.g., Ro-31-7549, Ro-31-8161, and Ro-31-8220), protein synthesis antagonists (e.g., Calcitriol, Du-026325, LG-1069, LG-1064, AGN-190168, Namirotene, and CBS-211A), purine nucleoside phosphorylase inhibitors (e.g., BCX-34), radical formation agonists (e.g., benzoporphyrin derivative), recombinant antileukoproteinases (e.g., ALP-242), retinoids (e.g., BMY-30123, LG-1069, and LG-1064), retinoid derivatives (e.g., AGN-190168), rapamycin binding proteins (FKBP) (e.g., immunophilins, VX-10367, and VX-10428), second generation monoaromatic retinoids (e.g., Acitretin, and Neotigason),

soluble IL-1, IL-4 and IL-7 receptors, somatostatin and somatostatin analogues (e.g., Octreotide, and Sandostatin), steroids, (e.g., AGN-191743), streptomyces anulatus isolates (e.g., epocarbazolin-A), superoxide dismutase (e.g., EC-SOD-B), thymidylate synthase inhibitors (e.g., AG-85, MPI-5002, 5-FU in biodegradable gel-like matrix, 5-FU and epinephrine in biodegradable gel-like matrix, and AccuSite), topical formulations (e.g., P-0751, and P-0802), transglutaminase inhibitors, tyrphostin EGF receptor kinase blockers (e.g., AG-18, and AG-555), VCAM-1 inhibitors (e.g., ISIS 3801), vitamin D analogues (e.g., Ro-23-6474, KH-1060, Calcipotriol, BMS-181161, BMY-30434, Dovonex, and Divonex), vitamin D_3 analogues (e.g., Tacalcitol, Bonealfa, TV-02 ointment), and vitamin D_3 derivatives (e.g., 1,2-diOH-vitamin D_3), and the like;

diabetes agents, such as ACE inhibitors (e.g., captopril), amylin, amylin agonists and antagonists (e.g., Normylin™, AC137, GC747, AC253, and AC625), autoimmune compounds (e.g., AI-401), capsaicins (e.g., Zostrix-HP), cell regulators (e.g., protein kinase C inhibitors, and Balanol), domperidones (e.g., Motilium®), fluvastatins (e.g., Lescol), FOX 988, fusion toxins (e.g., DAB_{389}IL-2, and DAB_{486}IL-2), gene therapies (e.g., Transkaryotic Therapies), glucagons (e.g., recombinant yeast glucagon), IL-10 compounds, iloprost, immunosuppressives (e.g., tacrolimus, Prograf, and FK-506), proinsulin, insulin and insulin analogs (e.g., AI-401, Nu-Insulin compounds, Humulin, Iletin, Humalog™, LYs-Pro, and Amaryl), insulin-like growth factors (e.g., Chiron/Ciba-Geigy compounds, Fujisawa compounds, and Genetech compounds), insulinotropins (e.g., Pfizer/Scios Nova compounds), nerve growth factors (e.g., Genentech compounds), oral hypoglycemics (e.g., AS-6, glimepiride, Amaryl, CL 316,243, acarbose, miglitol, recombinant yeast glucagon, GlucaGen™, NovoNorm™, glipizide, insulinotropin, and CI-991/CS-045), platelet-derived growth factors (e.g., Zymo Genetics/Novo Nordisk compounds), sulfonylureas (e.g., tolbutamide,

acetohexamide, tolazamide, and chlorpropramide), T cell approaches (e.g., anergize, AnergiX™, Procept compounds, and T cell Sciences compounds), and tolrestats (e.g., Alredase®, and ARI-509), activin, somatostatin, and the like;

stroke agents, such as 5-HT antagonists (e.g., Piperazine derivative), 5-HT reuptake inhibitors (e.g., Milnacipran, and Dalcipran), 5-HT 1A agonists (e.g., SR-57746A, and SR-57746), 5-HT 3 agonists (e.g., SR-57227), 5-HT 4 antagonists, 5-lipoxygenase inhibitors (e.g., low MW dual 5-lipoxygenase and PAF inhibitor CMI-392), ACh agonists (e.g., Pramiracetam, Choline-L- alfoscerate, L-alpha-glycerylphosphoryl-choline, and Delecit), adenosine agonists (e.g., GP-1-4683, ARA-100, and arasine analogs), adenosine A1 receptor agonists (e.g., Azaisotere, 2-chloro-N-[4 (phenylthio)-1-piperidinyl] adenosine, and 2120136), adenosine reuptake inhibitors (e.g., Diphenyloxazole derivatives), adrenergic transmitter re-uptake inhibitors (e.g., Bifemelane, E-0687, MCI-2016, Alnert, and Celeport), aldose reductase inhibitors (e.g., Spiro-3' pyrroline derivatives), alpha antagonists (e.g., Drotaverine acephyllinate, and Depogen), alpha 2 agonists (e.g., SNAP-5083, SNAP-5608, and SNAP-5682), AMPA receptor agonists (e.g., heterocyclic compound SYM-1207, and heterocyclic compound SYM-1252), AMPA receptor antagonists (e.g., LY-293558, and LY-215490), Ancrod/Arvin, aspirin, benzothiazoles (e.g., Lubeluzole, and R87926), benzodiazepine receptor antagonists (e.g., 3-oxadiazolyl-1,6-naph-thyridine derivatives, Tetracyclic imidazodiazepineseries imidazenil, FID-02-023, and Ro-23-1412), blood substitutes, bradykinin antagonists (e.g., CP-0127, Bradycor, and Septicor), C5a release inhibitors (e.g., protein derivative CMI-46000), calcium antagonists (e.g., Lemildipine, NB-818, NPK-1886, Trimetazidine derivative, Iomerizine KP-2796, Diltiazem analog clentiazem maleate, and TA-3090), calcium channel antagonists (e.g., nitrendipine-like compound diperdipine, YS-201, U-92032, Diltiazem

derivative, 1058, SM-6586, KP-840, F-0401, D-31-D, Tetrahydronaphthalene derivatives, fasudil, AT-877, H-7, HA-1044, HA-1077, Eril, darodipine, dazodipine, PY-108-068, Plimo, Dihydropy-ridine, AE 0047, GJ-0956, Lacidipine, GR-43659, GR-43659X, GX-1048, S-312-d, S-312, S-830312, Nilvadipine, and FK-235), calpain inhibitors (e.g., AK-275, and CX-275), carnitine palmitoyl-transferase inhibitors, carvedilol, cerebral calcium antagonist vasodilators (e.g., Nimodipine, and Nimotop), cholinesterase inhibitors (e.g., indole and indazole derivatives, and Tacrine analog), complement factor inhibitors (e.g., TK9C, protein derivative TP16, compinact A, compinact C, Factor D inhibitors, and soluble, recombinant MCP-based complement inhibitors), complement inhibitors (e.g., sCRI/BRL-55730, and YM-203), coronary vasodilators (e.g., Nicorandil, RP-46417, SG-75, and Adancor), CPC-111, cytidyl diphosphocholine/citicholines, cytokines (e.g., NBI-117), Dexanabiol, dopamine agonists, EAA receptors, endothelin antagonists (e.g., SB 209670), endothelin receptor antagonists, excitatory amino acid agonists (e.g., acylated polyamine analogs, and N-(4-hydroxyphenylpropa-nonyl)-spermine analog), excitatory amino acid antagonists (e.g., Tryptophan, 4,6-disubstituted stroke & kynurenine derivatives, NPC-17742, CPC-701, and CPC-702), glutamate antagonists (e.g., Kainate quisqualate NNC-07-9202, NPC-17742, small molecule CNS-1237, NS-257, NS-072, BW-619C, CGS 19755, Riluzole, PK-26124, and RP 54274), glutamate receptor antagonists (e.g., Araxin compounds, Quinoxaline derivative, YM-90K, and YM-900), glycine antagonists, glycine NMDA agonists (e.g., 3-hydroxy-2,5-dioxo-1H-benz[b]azepines), glycine NMDA associated antagonists (e.g., 5,6-dihydro-1H-pyrrolo [1,2,3-de] quinoxaline-2,3-diones, Strychnine-insensitive glycine binding site of NMDA receptor L-687414, Glystasins, ACEA-2011, ACEA-3031, AC-1021, ACPC, and eliprodil), growth factor antagonists (e.g., non-peptide indolocarbazole neutrophic molecules, and CEP-075),

GPIIb/IIIa antagonists (e.g., Peptide C68-22), hemorheological agents (e.g., Drotaverine acephyllinate, and Depogen), heparin, hydroxyl radical formation inhibitors (e.g., homopiperazine derivative K-7259), hypocalcemic agents (e.g., calcitonin peptide, related to hCGRP peptide), hypothermic agents/BMY-20862, ICAM-1 compounds (e.g., Enlimomab), immunosuppressants (e.g., small molecule compounds, and NBI-117), integrin general antagonists (e.g., monoclonal antibody AN-100225, and monoclonal antibody AN-100226), Interleukin-1 antagonists (e.g., cyclic nitrones), iron-dependent lipid peroxidation inhibitors (e.g., 2-(amino-methyl) chromans), lactic acid accumulation/inhibitors (e.g., small molecule CPC-211), Leukotriene B4 antagonists (e.g., Ebselen, DR-3305, PZ-25, PZ-51, RP 60931, and RP 61605), lipid peroxidase inhibitors (e.g., Idebenone, and Avan), low molecular weight small molecules, methyltransferase stimulants (e.g., 4-methyl benzenesulfonate, ademetionine sulfate tosilate, FO-156, and Ceritan), monoamine oxidase B inhibitors (e.g., MD-280040, MD-200243, MD-280080, Lazabemide, and Ro-19-6327), MS-153, MS-424, /Na^+/H^+ Na^+/Li^+ exchange inhibitors (e.g., Pyrazine derivatives), nadroparin (e.g., Fraxiparin), nafronyl/naftidrofuryl (e.g., Praxilene), nerve growth factor agonists (e.g., small molecule compounds, CNTF, BDNF, 2.5S NGF, monosialoganglioside GM1, and Sigen/Sygen), neuronal calcium channel blockers (e.g., CPC-304, and CPC-317), neuronal differentiation compounds (e.g., F-spondin), neuropeptide agonists (e.g., Neurotrophic Peptide Trofexin), neutrophil inhibitory factors (e.g., small molecule compounds), nitric oxide agonists (e.g., hydroxy derivative N-3393, hydroxy derivative N-3398, nicorandil, and Therapicon), nitric oxide antagonists, NMDA antagonists (e.g., Spiroisoindoles/dizocilpine derivatives, Oxindole compound, CP-112116, LY-104658, LY-235959, FR-115427, Sialic acid derivative, N-palmitoyl-Betaethylglycoside neuraminic acid, ND-37, Ro-01-6794, 706, Dextrorphan, Ifenprodil analogue eliprodil, SL-82.0715, Lipophilic

molecules, HU-211, Remacemide, 934-423, 12495, 12859, 12942AA, Selfotel, CGS-19755, SDZ-EAA-494, CGP-40116, CGP-37849, CGP-39551, and CGP-43487), NMDA antagonist-partial agonists (e.g., Conantokin G peptide SYM-1010), NMDA channel blockers (e.g., Aptiganel, CERESTAT, and CNS 1102), NMDA receptor antagonists, NMDA receptor subtypes (e.g., Kainate quisqua-late NNC-07-9202), non-competitive NMDA antagonists (e.g., FPL-15896), non-ionic copolymer RheothRx, nootropic/acetylcholine agonists (e.g., Oxiracetam, CT-848, and Neuractiv), norepinephrine inhibitors (e.g., Midalci-pran), N-type calcium channel antagonists (e.g., NS-626, and NS-638), opioid antagonists (e.g., Nalmefene, nalmetrene, JF-1, ORF-11676, Cervene, and Incystene), opioid kappa receptor agonists (e.g., acrylacetamide enadoline, and CI-997), organoselenims (e.g., Ebselen, DR-3305, PZ-25, PZ-51, RP 60931, and RP 61605), oxygen scavengers (e.g., Tirilazad mesylate, Lazaroids, and Freedox), PA2 inhibitors (e.g., phospholipase A2 inhibitor), PAF antagonists (e.g., nupafant, and BB-2113), partial glycine NMDA agonists (e.g., ACPC), peptide/ GPIIb/IIIa antagonists (e.g., Integrelin), peptidic neuron-specific calcium channel antagonists (e.g., SNX-111), phosphodiesterase inhibitors (e.g., Xanthine derivatives, propentofylline, Hoe-285, and Hextol), phospholipase A2 inhibitors (e.g., small organic molecule CEP-217), plasminogen activators (e.g., r-ProUK (recombinant pro-urokinase), platelet-activating factor antagonists (e.g., UK-74505), platelet adhesion inhibitors (e.g., Peptide), platelet aggregation antagonists (e.g., cilostazol, peptide agents, GPHb-IIIA inhibitor, and TP-9201), platelet aggregation inhibitors (e.g., Diaminoalkanioic acid derivatives), potassium channel agonists (e.g., Nicorandil, RP-46417, SG-75, and Adancor), prolyl endopeptidase (PEP) inhibitors (e.g., JTP-4819), protein kinase C inhibitors (e.g., monosialoganglioside derivative Liga-20), proteolytic enzyme inhibitors (e.g., Protease nexin-1, Incyte, PN-1, PN-2, Nafamostat, FUT-175, Duthan, and

Futhan), pyrimidine derivatives, Quinolizine derivatives (e.g., KF-17329, and KF-19863), radical formation antagonists (e.g., EPC-K1), recombinant tissue plasminogen activators (e.g., alteplase, and Activase), Schwann cell derived molecules/promoters, sigma antagonists (e.g., Sigma ligand), sigma receptor antagonists (e.g., tetrahyropyridinyl-isoxazolines and isoxazoles PD-144418), sodium/calcium channel modulators (e.g., Lifarizine, and RS-87476), sodium channel antagonists, streptokinase (e.g., Streptase), substituted guanadine (e.g., small molecule CNS-1237), superoxide dismutase stimulants (e.g., PEG conjugated enzyme superoxide dismutase/Dismutec, and PEG-SOD), thrombin inhibitors, (e.g., non-peptide), thromboxane synthase inhibitors (e.g., Linotroban, and HN-11500), thyrotropin-releasing hormone agonists (e.g., TRH agonists, Protirelin analogthymoliberin, and RX-77368,), ticlopidine (e.g., Ticlid), TJ-8007, TRH agonists (e.g., Thyrotropin releasing hormones, and JTP-2942), trilazard, urokinase (e.g., Abbokinase), w-conopeptide (e.g., SNX-111), and warfarin (e.g., Coumadin), and the like;

agents useful for the treatment of carcinomas (e.g., adriamycin, taxol, interleukin-1, interleukin-2 (especially useful for treatment of renal carcinoma), and the like, as well as leuprolide acetate, LHRH analogs (such as nafarelin acetate), and the like, which are especially useful for the treatment of prostatic carcinoma),

agents useful for the treatment of endometriosis (e.g., LHRH analogs),

agents useful for the treatment of uterine contraction (e.g., oxytocin),

agents useful for the treatment of diuresis (e.g., vasopressin),

agents useful for the treatment of cystic fibrosis (e.g., Dnase (i.e., deoxyribonuclease), SLPI, and the like),

agents useful for the treatment of neutropenia (e.g., GCSF),

agents useful for the treatment of lung cancer (e.g., beta 1-interferon),

agents useful for the treatment of respiratory disorders (e.g., superoxide dismutase),

agents useful for the treatment of ischemia/reperfusion injury (e.g., selectin inhibitors,

Irf1, and the like);

agents useful for the treatment of osteoporosis (e.g., statins, such as lovastatin, pravastatin, atorvastatin, and the like; bisphosphonates; and the like);

nitric oxide synthase inhibitors (e.g., N^4-methyl-L-arginine, aminoguanidine, N^4-(iminoethyl)-L-ornithine, thiocitrulline and other citrulline derivatives, N^4-nitro-L-arginine, N^4-nitro-L-arginine methyl ester, N^4-amino-L-arginine, and other arginine derivatives, isothiourea and its derivatives, and the like,

as well as a variety of other agents, such as acyclovir, alendronate sodium, amlodipine, ampicillin, azelaic acid, azithromycin, beclomethasone, betamethasone, bicalutamide, buspirone, carisoprodol, carvedilol, cefaclor, cefadroxil, cefixime, cefprozil, ceftibuten, cefuroxime axetil, cephalexin, cetirizine hydrochloride, cimetidine, ciprofloxacin, cisapride, clarithromycin, clavulanate, clonazepam, clotrimazole, codeine, conjugated estrogens, cyclobenzaprine, desogestrel, dexrazoxane, diazepam, dicyclomine HCl, digoxin, diltiazem, dirithromycin, doxazosin, doxycycline, enalapril, erythromycin, erythromycin base, erythromycin stearate, estradiol, ethinyl estradiol, ethynodiol diacetate, etodolac, famotidine, fluconazole, fluoxetine, fluvastatin, furosemide, gemfibrozil, glipizide, glyburide, guaifenesin, hydrochlorothiazide, hydrocodone, hydrocortisone, ibuprofen, ibutilide fumarate, indapamide, insulin, ipratropium bromide, ketoconazole, ketoprofen, ketorolac tromethamine, lamivudine, lansoprazole, levonorgestrel, levothyroxine, lisinopril, loracarbef, loratidine, lorazepam, losartan potassium, lovastatin, medroxyprogestrone, methylphenidate, methylprednisolone, metoprolol, metoprolol tartrate, moexipril hydrochloride, mometasone furoate, mupirocin, mycophenolate mofetil, nabumetone, nalmefene hydrochloride, naproxen, neomycin, nifedipine, nisoldipine, nitrofurantoin, nizatidine, norethindrone, norgestrel, nortriptyline, ofloxacin, omeprazole, oxaprozin, oxycodone, paroxetine, penicillin, pentoxifylline, phenylpropanolamine, phenytoin, polymyxin, porfimer sodium, potassium chloride, pravastatin, prednisone, promethazine, propoxyphene, pseudoephedrine, quinapril, ramipril, ranitidine, riluzole, salmeterol, saquinavir mesylate, sertraline, sevoflurane, simvastatin, sucralfate, sulfamethoxasole, sumatriptan, temazepam, terazosin, terconazole, terfenadine, tetracycline, theophylline, timolol,

tramadol, tramadol hydrochloride, tretinoin, triamcinolone acetonide, triamterene, trimethoprim, valproic acid, venlafaxine, verapamil, wafarin, zolpidem, and the like.

The dithiocarbamate component and the pharmocalogically active agent of invention conjugates are indirectly covalently attached employing a variety of linkages (including a linker), e.g., ester linkages, disulfide linkages, amide linkages, ether linkages, thioether linkages, imide linkages, sulfate ester linkages, sulfonate ester linkages, phosphate ester linkages, carbonate linkages, O-glycosidic linkages, S-glycosidic linkages, and the like. Such linkages can be accomplished using standard synthetic techniques as are well known by those of skill in the art, either by direct reaction of the starting materials, or by incorporating a suitable functional group on the starting material, followed by coupling of the reactants.

Linker, L (also referred to herein as linker/spacer) contemplated for use herein includes moieties having the structure -Y-W-,
wherein:

Y is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

W=O, N, P or S.

Modifying groups contemplated for use in the practice of the present invention include:

$-CR_3$, $-SiR_3$,

$-NR'_2$, $-PR'_2$,

$-OR''$, $-SR''$,

wherein:

each R is independently alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, acyl, substituted acyl, hydroxy, alkoxy, or substituted alkoxy;

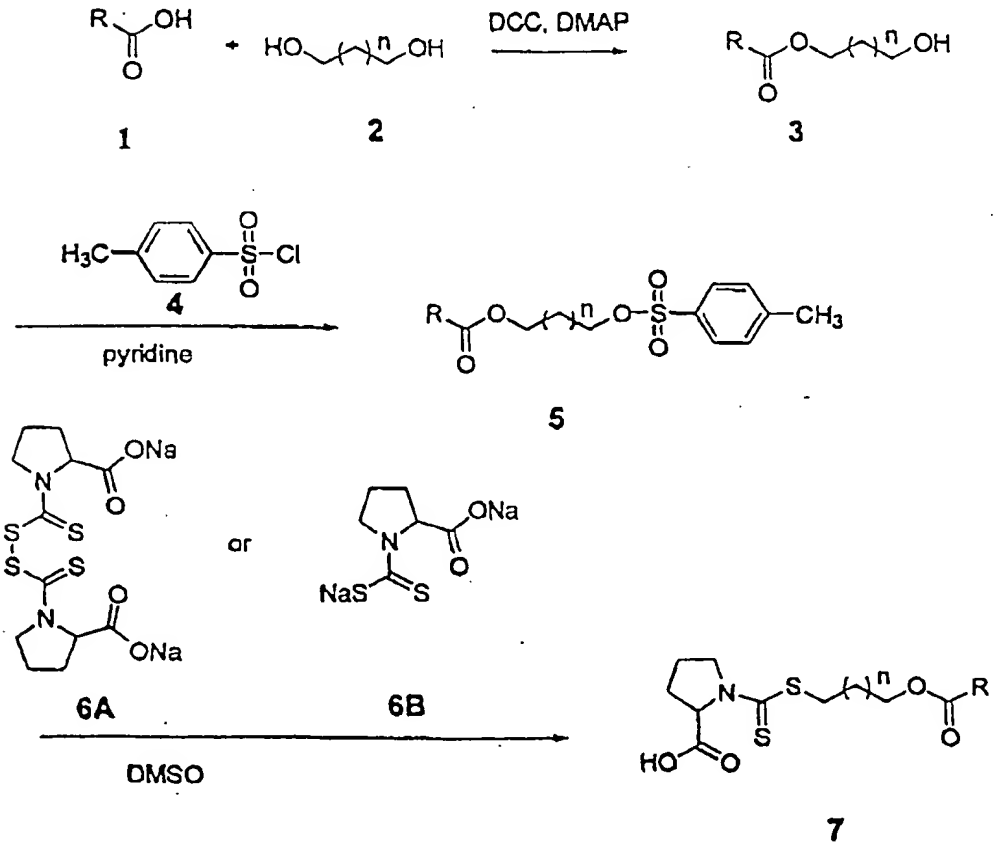
each R' is independently alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, acyl, substituted acyl, hydroxy, alkoxy, or substituted alkoxy; and

R" is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, acyl or substituted acyl.

In accordance with another embodiment of the present invention, there are provided methods for the preparation of protected forms of pharmacologically active agents, said method comprising covalently attaching a dithiocarbamate to said pharmacologically active agent. The resulting conjugate provides a latent form of the pharmacologically active agent, releasing the biological activity thereof only when the pharmacologically active component of said conjugate (including the linker referred to above) is cleaved from said conjugate (e.g., by an esterase, amidase or other suitable enzyme).

As readily recognized by those of skill in the art, invention conjugates can be prepared in a variety of ways. See, for example, Scheme 1, wherein a pharmacologically active compound (1) bearing a carboxylic moiety can be reacted with a diol (2) under conditions suitable to produce ester (3), which can then be activated by treatment with an arylsulfonyl chloride under conditions suitable to produce compound (5), which can then be coupled with the salt form of a dithiocarbamate (e.g., compound 6B or disulfide thereof such as compound 6A) to produce invention conjugate (7).

SCHEME 1



Employing this general reaction scheme, invention conjugates can be prepared from a wide variety of pharmacologically active agents. See, for example, Examples 6-13 provided herein.

In accordance with yet another embodiment of the present invention, there are provided methods for reducing the side effects induced by administration of pharmacologically active agent(s) to a subject, said method comprising covalently attaching a dithiocarbamate to said pharmacologically active agent(s) prior to administration to said subject.

In accordance with still another embodiment of the present invention, there are provided methods for enhancing the effectiveness of pharmacologically active agent(s), said method comprising covalently attaching a dithiocarbamate to said pharmacologically active agent.

In accordance with a still further embodiment of the present invention, there are provided improved methods for the administration of pharmacologically active agent(s) to a subject for the treatment of a pathological condition, the improvement comprising covalently attaching a dithiocarbamate to said pharmacologically active agent prior to administration of said pharmacologically active agent to said subject.

Those of skill in the art recognize that the conjugates described herein can be delivered in a variety of ways, such as, for example, orally, intravenously, subcutaneously, parenterally, rectally, by inhalation, and the like.

Depending on the mode of delivery employed, the conjugates contemplated for use herein can be delivered in a variety of pharmaceutically acceptable forms. For example, the conjugate can be delivered in the form of a solid, solution, emulsion, dispersion, micelle, liposome, and the like.

Thus, in accordance with still another embodiment of the present invention, there are provided physiologically active composition(s) comprising invention conjugates in a suitable vehicle rendering said conjugates amenable to oral delivery, transdermal delivery, intravenous delivery, intramuscular delivery, topical delivery, nasal delivery, and the like.

Pharmaceutical compositions of the present invention can be used in the form of a solid, a solution, an emulsion, a dispersion, a micelle, a liposome, and the like, wherein the resulting composition contains one or more of the compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for enteral or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The carriers which can be used include glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea, medium chain length triglycerides, dextrans, and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form. In addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound(s) (e.g., one or more pharmacologically active agents, covalently bound to a dithiocarbamate of structure **I**) is(are) included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or disease condition.

Pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of a sweetening agent such as sucrose, lactose, or saccharin, flavoring agents such as

peppermint, oil of wintergreen or cherry, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients may also be manufactured by known methods. The excipients used may be, for example, (1) inert diluents such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents such as corn starch, potato starch or alginic acid; (3) binding agents such as gum tragacanth, corn starch, gelatin or acacia, and (4) lubricating agents such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Pat. Nos. 4,256,108; 4,160,452; and 4,265,874, to form osmotic therapeutic tablets for controlled release.

In some cases, formulations for oral use may be in the form of hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

The pharmaceutical compositions may be in the form of a sterile injectable suspension. This suspension may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or

diglycerides, fatty acids (including oleic acid), naturally occurring vegetable oils like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or synthetic fatty vehicles like ethyl oleate or the like. Buffers, preservatives, antioxidants, and the like can be incorporated as required.

Conjugates contemplated for use in the practice of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Since individual subjects may present a wide variation in severity of symptoms and each drug has its unique therapeutic characteristics, the precise mode of administration and dosage employed for each subject is left to the discretion of the practitioner.

In general, the dosage of invention conjugate employed as described herein falls in the range of about 0.01 mmoles/kg body weight of the subject/hour up to about 0.5 mmoles/kg/hr. Typical daily doses, in general, lie within the range of from about 10 □g up to about 100 mg per kg body weight, and, preferably within the range of from 50 □g to 10 mg per kg body weight and can be administered up to four times daily. The daily IV dose lies within the range of from about 1 □g to about 100 mg per kg body weight, and, preferably, within the range of from 10 □g to 10 mg per kg body weight.

In accordance with yet another embodiment of the present invention, there are provided improved methods for the treatment of a subject suffering from a pathological condition by administration thereto of pharmacologically active agent(s), the improvement comprising covalently attaching a dithiocarbamate to said pharmacologically active agent prior to administration thereof to said subject.

Thus, invention method for the treatment of a subject afflicted with a pathological condition comprises administering to a subject an effective amount of a modified pharmacologically active agent,

wherein said pharmacologically active agent is effective for treatment of said condition, and

wherein said pharmacologically active agent has been modified by the covalent attachment thereto of a dithiocarbamate.

The invention will now be described in greater detail by reference to the following non-limiting examples.

EXAMPLE 1

Preparation of an ester conjugate of pyrrolidinol and ibuprofen.

To 200 ml of methylene chloride in a 500-ml reaction vessel was added 24 grams of ibuprofen (α- methyl-4-(2-methylpropyl)benzene-acetic acid), 10 grams of 2-pyrrolidinol and 0.5 grams of a suitable coupling agent, e.g., dicyclohexylcarbodiimide. The reaction proceeds at room temperature for 1 to 3 hours with stirring. The ester conjugate is isolated and purified with a 60-70% yield.

EXAMPLE 2

Conversion of an ester conjugate of pyrrolidinol and ibuprofen to an ester conjugate of pyrrolidinol dithiocarbamate and ibuprofen.

To 100 ml of methanol in a 500-ml reaction vessel was added 10 grams of the ester conjugate obtained from Example 1. An aqueous NaOH solution (6.9 grams in 10 ml water) is added dropwise to the reaction mixture at 4°C. The reaction is allowed to proceed for one additional hour at 4°C. A solution mixture of carbon

disulfide (5 ml) and ethanol (15 ml) is added dropwise to the above reaction mixture with slow stirring at 4°C. The final product is isolated and purified with a yield of about 70%.

EXAMPLE 3

Preparation of an ester conjugate of L-proline and adriamycin.

To 200 ml of methylene chloride in a 500-ml reaction vessel was added 47.2 grams of adriamycin, 10 grams of L-proline and 0.5 grams of any suitable coupling agent, e.g., dicyclohexylcarbodiimide. The reaction is allowed to proceed at room temperature for 1 to 3 hours with stirring. The ester conjugate is isolated and purified with about 70% yield.

EXAMPLE 4

Conversion of an ester conjugate of L-proline and adriamycin to an ester conjugate of L-proline dithiocarbamate and adriamycin.

To 100 ml of methanol in a 500-ml reaction vessel was added 10 grams of the ester conjugate obtained from Example 3. An aqueous NaOH solution (6.9 grams in 10 ml) water is added dropwise to the reaction mixture at 4°C. The reaction is allowed to proceed for one additional hour at 4°C. A solution mixture of carbon disulfide (5 ml) and ethanol (15 ml) is added dropwise to the above reaction mixture with slow stirring at 4°C. The final product is isolated and purified with a yield of about 70%.

EXAMPLE 5

General Procedure for the Preparation of Invention Conjugates.

5A. General procedure for the preparation of intermediate 3 (Scheme 1). To a stirring solution of pharmacologically active compound (1) (1 eq), diol compound (2) (5eq) and dimethylaminopyridine (DMAP) (0.2 eq) in anhydrous THF is added 1,3-dicyclohexylcarbodiimide (DCC) (1 eq) at 0°C. The resulting solution is stirred at room temperature for several hours. The reaction solution is filtered and the solvent is evaporated. The residue is partially dissolved in ethyl acetate and the solid is filtered off and the solution is washed with 0.5 N HCl , saturated sodium bicarbonate solution and brine. After the solvent is evaporated, the compound is purified either by flash chromatography or recrystallization to give compound **3**.

5B. General procedure for the preparation of intermediate 4 (Scheme 1). To a solution of compound **3** (1eq) in pyridine is added *p*-toluenesulfonyl chloride (**4**) (2 eq) at 0°C. The resulting solution is put in the refrigerator (~4°C) for three days. The reaction solution is poured onto ice and extracted with ether. The combined ether solution is washed with water and dried. After the solvent is evaporated, the residue is purified by appropriate means to give compound **5**.

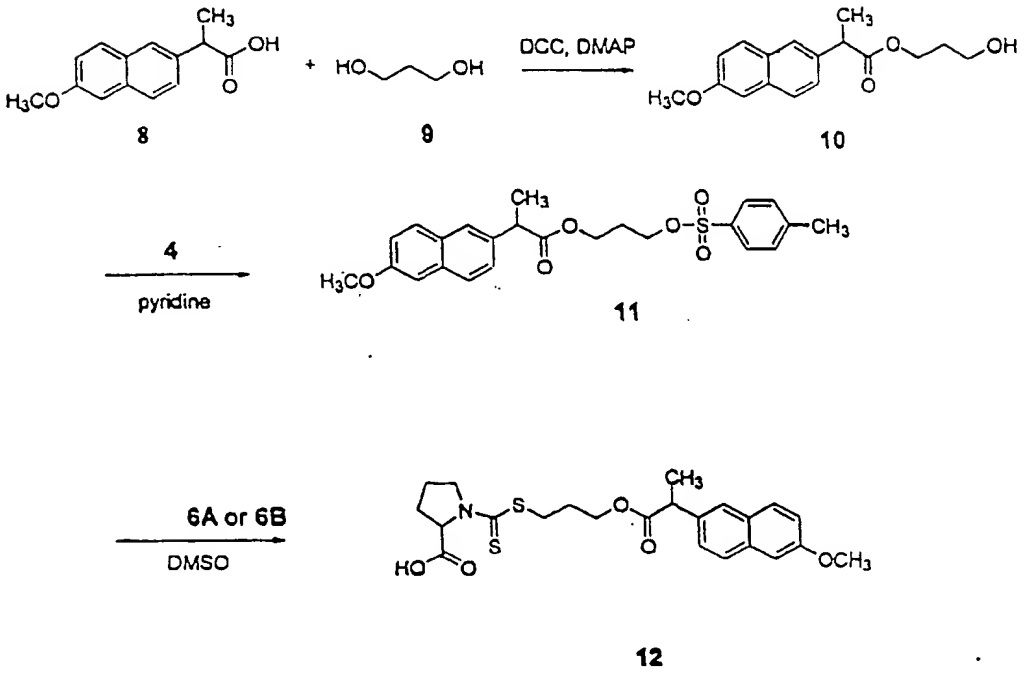
5C. General procedure for the preparation of conjugate compound 7 (Scheme 1). A solution of intermediate **5** and compound **6A** or **6B** in DMSO is stirred at room temperature under argon for one to three hours. The reaction solution is poured onto ice and extracted with ether. The combined ether solution is washed with water. The ether is dried and evaporated and the residue is purified by appropriate means to give the conjugate compound **7**.

EXAMPLE 6

Synthesis of Invention Conjugate of Naproxen.

The synthetic steps described in this example are illustrated in Scheme 2:

SCHEME 2



6A. 3-Hydroxypropyl (*S*)-(+)-methoxy-α-methyl-2-naphthaleneacetate 10 (Scheme 2). To a stirring solution of (*S*)-(+)-methoxy-α-methyl-2-naphthaleneacetic acid (naproxen, 8) (10.4 g, 45 mmol), propanediol (9) (17.1 g, 225 mmol) and DMAP (0.54 g, 4.5 mmol) in anhydrous THF (300 mL) is added DCC (9.4

g, 45 mmol) at 0°C. The resulting solution is stirred at 0°C for 10 min and then at room temperature for 5h. The reaction solution is filtered and the solvent is evaporated. The residue is partially dissolved in ethyl acetate and the solid is filtered off and the solution is washed with 0.5 N HCl, saturated sodium bicarbonate solution and brine. The organic phase is dried (Na_2SO_4) and the solvent is evaporated. The residue is purified by recrystallization from 1:3 hexanes-dichloromethane to give 9.7 g (75%) of compound **10** as a white solid; ^{1}H NMR ($CDCl_3$) □ 1.58 (d, 3H), 1.78 (m, 2H), 1.88 (t, 1H, ex D_2O), 3.53 (m, 2H), 3.87 (q, 1H), 3.90 (s, 3H), 4.2 (m, 2H), 7.11-7.15 (m, 2H), 7.39 (d, 1H), 7.65 (s, 1H), 7.70 (d, 2H); MS (ES) *m/z* 289.2 $(M + H)^+$ ($C_{17}H_{22}O_4$ requires 289.34).

6B. 3-Tosylpropyl (*S*)-(+)-methoxy-□-methyl-2-naphthaleneacetate 11 (Scheme 2). To a stirring solution of compound **10** (8.6 g, 30 mmol) in 35 mL of pyridine is added tosyl chloride (4) (11.43 g, 60 mmol) at 0°C. The resulting solution is put in the refrigerator (~4°C) for three days. The reaction solution is poured onto 300 g ice and extracted with ether. The combined ether solution is washed with 10% HCl solution, saturated $NaHCO_3$ solution and brine. The solution is dried (Na_2SO_4) and evaporated. The residue is purified by flash chromatography on a silica gel column using 100% CH_2Cl_2 as the eluent to give 8.92 g (67%) of compound **11** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) □ 1.53 (d, 3H), 1.90 (m, 2H), 2.42 (s, 3H), 3.78 (q, 1H), 3.91 (s, 3H), 3.99 (m, 1H), 4.09 (t, 2H), 7.11-7.15 (m, 2H), 7.25-7.28 (m, 2H), 7.32-7.34 (m, 1H), 7.64 (m, 1H), 7.65-7.71 (m, 4H); MS (ES) *m/z* 443.3 $(M + H)^+$ ($C_{24}H_{27}O_6S$ requires 443.53).

6C. Compound 12 from Compound 6A (Scheme 2). To a stirring solution of compound **11** (8.86 g, 20.02 mmol) in 35 mL of DMSO is added compound **6A** (3.86 g, 9.1 mmol) at room temperature. The resulting solution is stirred at room temperature for 70 min. The reaction solution is poured onto 100 g ice and extracted with ether. The combined ether solution is washed with water and brine. The solution is dried (Na_2SO_4) and evaporated. The residue is purified by flash chromatography on a silica gel column using 200:1 and then 20:1 CH_2Cl_2-CH_3OH as

eluents to give 3.74g (45%) of compound **12** as a white foam; ^{1}H NMR ($CDCl_3$) □ 1.57(d, 6H), 1.94-2.20 (m, 12H), 3.20-3.25 (m, 4H), 3.57-3.59 (m, 2H), 3.72-3.79 (m, 2H), 3.84-3.88 (m, 2H), 3.90 (s, 6H), 5.05 (m, 2H), 7.10-7.14 (m, 4H), 7.39-7.41 (d, 2H), 7.65-7.70 (m, 6H); MS (ES) *m/z* 921.5 M^+ ($C_{46}H_{52}N_2O_{10}S_4$ requires 921.2).

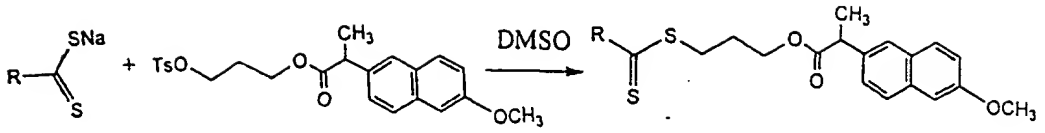
6D. Compound 12 from Compound 6B (Scheme 2). To a stirring solution of compound **5** (2.21g, 5mmol) in 10 mL of anhydrous DMSO is added compound **6B** (1.06, 4.5 mmol) at room temperature. The resulting solution is stirred at room temperature for 80 min. The reaction solution is poured into water and washed with ether. The aqueous solution is acidified to pH = 3-4 using concentrated HCl solution and extracted with dichloromethane. The combined organic phase is washed with water and brine. The organic phase is dried over Na_2SO_4 and the solvent is evaporated under high vacuum to give 1.3g (63%) of the compound **12.** Compound 12 from this procedure has the same ^{1}H NMR and MS spectra with the compound from the above procedure using compound **6A**.

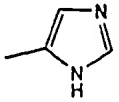
EXAMPLE 7

Alternate Synthetic Methods for Preparation of a Series of Conjugates of Naproxen.

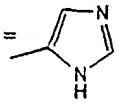
The naproxen derivatives described in this example are illustrated in Scheme 3.

SCHEME 3



13. R = CH_3
14. R = CH_2CH_3
15. R = C_6H_5
16. R = o-C_6H_4(OH)
17. R = 

11

18. R = CH_3
19. R = CH_2CH_3
20. R = C_6H_5
21. R = o-C_6H_4(OH)
22. R = 

7A. Compound 18 (Scheme 3) . To a stirring solution of compound **11** (8.84 g, 20.0 mmol) in 35 mL of DMSO was added compound **13** (2.28 g, 20 mmol) at rt. The resulting solution was stirred at rt for 2.5 h. The reaction solution was poured on to 100 g ice and extracted with ether. The combined ether solution was washed with water and brine. The solution was dried (Na_2SO_4) and evaporated. The residue was purified to give 70-80% yield of compound **18**.

7B. Compound 19 (Scheme 3). Compound **19** was prepared as described above for compound **18** from compound **11** (8.84 g, 20.0 mmol) in 35 mL of DMSO and compound **14** (2.56 g, 20 mmol). The reaction gave 70-80% yield of compound **19**.

7C. Compound 20 (Scheme 3). Compound **20** was prepared as described above for compound **18** from compound **11** (8.84 g, 20.0 mmol) in 35 mL of DMSO and compound **15** (3.52 g, 20 mmol). The reaction gave 70-80% yield of compound **20**.

7D. Compound 21 (Scheme 3). Compound **21** was prepared as described above for compound **18** from compound **11** (8.84 g, 20.0 mmol) in 35 mL of DMSO and compound **16** (3.84 g, 20 mmol). The reaction gave 70-80% yield of compound **21.**

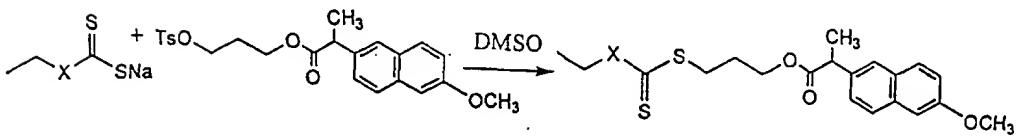
7E. Compound 22. Compound **22** was prepared as described above for compound **18** from compound **11** (8.84 g, 20.0 mmol) in 35 mL of DMSO and compound **17** (3.32 g, 20 mmol). The reaction gave 70-80% yield of compound **22.**

EXAMPLE 8

Additional synthetic Methods for Preparation of Conjugates of Naproxen.

The naproxin derivatives described in this example are illustrated in Scheme 4.

SCHEME 4



23. X = O
24. X = S

25. X = O
26. X = S

11

8A. Compound 25 (Scheme 4). Compound **25** was prepared as described above for compound **18** from compound **11** (8.84 g, 20.0 mmol) in 35 mL of DMSO and compound **23** (2.88 g, 20 mmol). The reaction gave 70-80% yield of compound **25.**

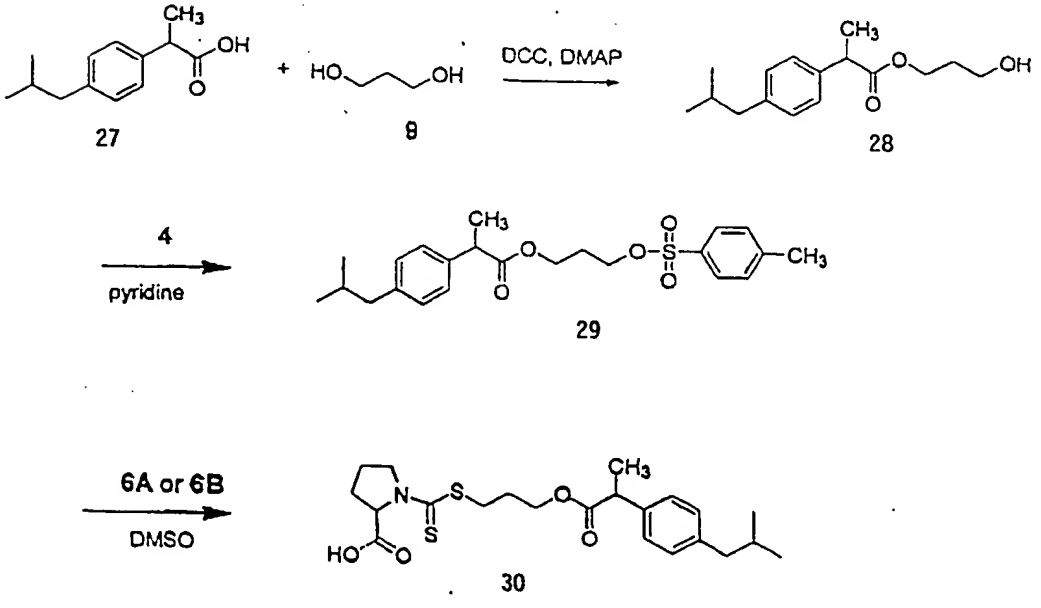
8B. Compound 26 (Scheme 4). Compound **26** was prepared as described above for compound **18** from compound **11** (8.84 g, 20.0 mmol) in 35 mL of DMSO and compound **24** (3.20 g, 20 mmol). The reaction gave 70-80% yield of compound **26**.

EXAMPLE 9

Synthesis of Invention Conjugate of Ibuprofen.

The synthetic steps described in this example are illustrated in Scheme 5:

SCHEME 5



9A. 3-Hydroxypropyl (*S*)-(+)-4-isobutyl-α-methylphenylacetate 28 (Scheme 5). Compound **28** is prepared as described above for compound **10** from (*S*)-(+)-4-isobutyl-α-methylphenylacetic acid (ibuprofen, **27**) (4.12g, 20 mmol) and propanediol (7.6 g, 100 mmol). The compound is purified by flash chromatography on a silica gel column using 10:1 and then 3:1 hexanes-ethyl acetate as eluents to give 3.54 g (65%) of compound **28** as a colorless oil; ^{1}H NMR ($CDCl_3$) □ 0.89 (d, 6H), 1.49 (d, 3H), 1.80 (m, 2H), 1.76-1.85 (m, 2H, 1H ex D_2O), 2.45 (m, 2H), 3.52 (m, 2H), 3.70 (q, 1H), 4.21 (m, 2H), 7.10 (d, 2H), 7.18 (d, 2H); MS (ES) *m/z* 265.7($M + H)^+$ ($C_{16}H_{25}O_3$ requires 265.36).

9B. 3-Tosylpropyl (*S*)-(+)-4-isobutyl-α-methylphenylacetate 29 (Scheme 5). Compound **29** is prepared as described above for compound **11** from compound **28** (1.76 g, 0.56 mmol) and tosyl chloride (4) (0.5 g, 1.13 mmol). The compound is purified by flash chromatography on a silica gel column using CH_2Cl_2 as the eluent to give 1.5 g (54%) of the compound **29** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.88 (d, 6H), 1.43 (d, 3H), 1.80-1.92 (m, 3H), 2.44 (d, 2H), 2.45 (s, 3H), 3.61 (q, 1H), 3.99 (t, 2H), 4.08 (t, 2H), 7.07 (d, 2H), 7.13 (d, 2H), 7.33 (d, 2H), 7.75 (d, 2H); MS (ES) *m/z* 441.3 $(M + Na)^+$ ($C_{23}H_{30}O_5SNa$ requires 441.55).

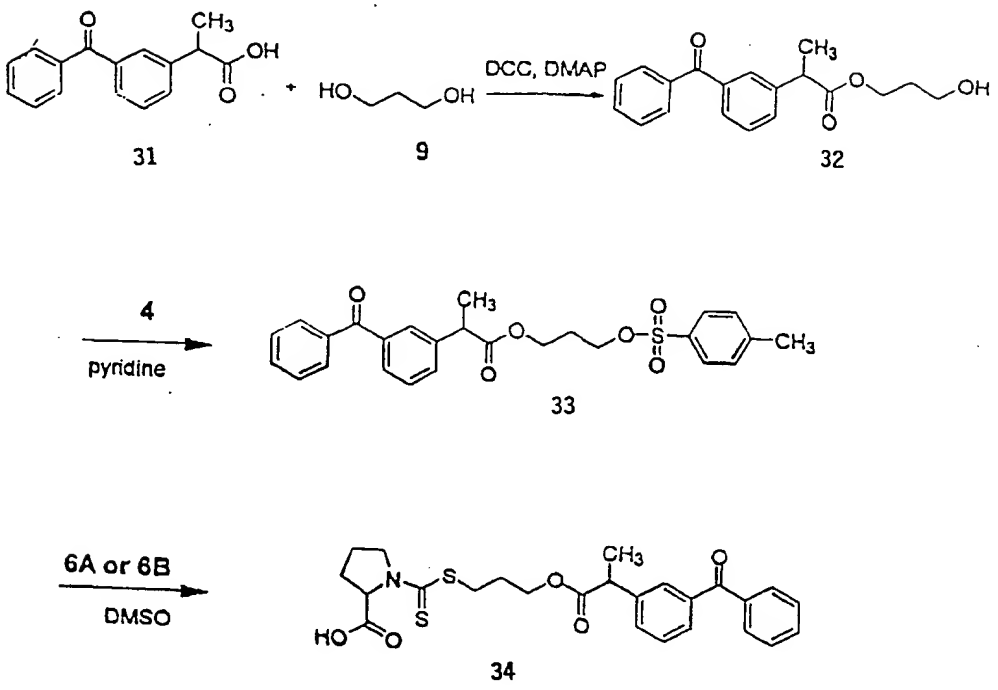
9C. Compound 30 (Scheme 5). Compound **30** is prepared as described above for compound **12** from compound **29** (1.35 g, 3.2 mmol) and compound **6A** (0.7 g, 1.6 mmol) or **6B** (0.75g, 3.3 mmol) in DMSO. The compound is purified by flash chromatography on a silica gel column using 200:1 and then 20:1 CH_2Cl_2-CH_3OH as eluents to give 0.55 g (40%) of compound **30** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.89 (d, 6H), 1.49 (d, 3H), 1.84 (m, 1H), 2.00 (m, 2H), 2.17-2.32 (m, 4H), 2.44 (d, 2H), 3.23 (m, 2H), 3.71 (m, 2H), 3.81 (m, 1H), 7.08 (d, 2H), 7.24 (d, 2H); MS (ES) *m/z* 873.2 M^+ ($C_{44}H_{60}N_2O_8S_4$ requires 873.22).

EXAMPLE 10

Synthesis of Invention Conjugate of Ketoprofen.

The synthetic steps described in this example are illustrated in Scheme 6:

SCHEME 6



10A. 3-Hyroxypropyl (*S*)-(+)-3-benzoyl-α-methylbenzeneacetate 32 (Scheme 6). Compound **32** is synthesized as described above for compound **10** from (*S*)-(+)-3-benzoyl-α-methylbenzeneacetic acid (ketoprofen, **31**) (3.8 g, 15 mmol) and propanediol (**9**) (5.7 g, 75 mmol). The compound is purified by flash chromatography on a silica gel column using 200:1 CH_2Cl_2-MeOH as the eluent to give 2.63 g (56%)

of the compound **32** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ1.54 (d, 3H), 1.82 (m, 2H), 1.82-1.82 (b, 1H, ex D_2O), 3.58 (m, 2H), 3.79-3.83 (q, 1H), 4.25 (m, 2H), 7.42-7.80 (m, 9H); MS (ES) *m/z* 313.1 $(M + H)^+$ ($C_{19}H_{21}O_4$ requires 313.3).

10B. 3-Tosylpropyl (*S*)-(+)-3-benzoyl-α-methylbenzeneacetate 33 (Scheme 6). Compound **33** is synthesized as described above for compound **11** from compound **32** (2.48 g, 7.94 mmol) and compound **4** (3.03 g, 15.9 mmol). The compound is purified by flash chromatography on a silica gel column using 6:1 and then 4:1 hexanes-ethyl acetate as eluents to give 2.72 g (74%) of the compound **33** as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 1.49 (d, 3H), 1.94 (m, 2H), 2.43 (s, 3H), 3.73 (q, 1H), 4.01 (t, 2H), 4.11 (t, 2H), 7.31-7.79 (m, 13H); MS (ES) *m/z* 467.3 $(M + H)^+$ ($C_{26}H_{27}O_6S$ requires 467.55).

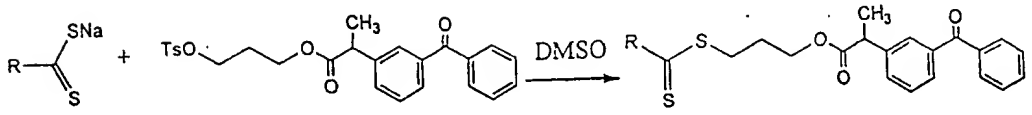
10C. Compound 34 (Scheme 6). Compound **34** is prepared as described above for compound **12** from compound **6A** (0.91 g, 2.15 mmol) **or 6B** (1.01g, 4.3 mmol) and compound **33** (2.0 g, 4.30 mmol) in 9 ml of DMSO. The compound is purified by flash chromatography on a silica gel column using 3:1 hexanes-ethyl acetate and then 20:1 CH_2Cl_2-MeOH as eluents to give 1.21 g (58%) of the compound **34** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.44 (d, 3H), 1.82-2.11 (m, 6H), 3.12-3.28 (m, 2H), 3.59-3.72 (m, 2H), 3.61-3.75 (m, 2H), 3.90-4.15 (m, 3H), 4.85 (m, 1H), 7.51-7.73 (m, 9H); MS (ES) *m/z* 969.5 $(M + H)^+$ ($C_{50}H_{53}N_2O_{10}S_4$ requires 969.22).

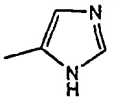
EXAMPLE 11

Alternate Synthetic methods for Preparation of a Series of Conjugates of Ketoprofen.

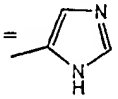
The ketoprofen derivatives described in this example are illustrated in Scheme 7.

SCHEME 7



35. R = CH_3
36. R = CH_2CH_3
37. R = C_6H_5
38. R = o-C_6H_4(OH)
39. R = 

33

40. R = CH_3
41. R = CH_2CH_3
42. R = C_6H_5
43. R = o-C_6H_4(OH)
44. R = 

11A. Compound 40 (Scheme 7). Compound **40** was prepared as described above for compound **18** from compound **33** (9.32 g, 20.0 mmol) in 35 mL of DMSO and compound **35** (2.28 g, 20 mmol). The reaction gave 70-80% yield of compound **40**.

11B. Compound 41 (Scheme 7). Compound **41** was prepared as described above for compound **18** from compound **33** (9.32 g, 20.0 mmol) in 35 mL of DMSO and compound **36** (2.56 g, 20 mmol). The reaction gave 70-80% yield of compound **41**.

11C. Compound 42 (Scheme 7). Compound **42** was prepared as described above for compound **18** from compound **33** (9.32 g, 20.0 mmol) in 35 mL of DMSO and compound **37** (3.52 g, 20 mmol). The reaction gave 70-80% yield of compound **42.**

11D. Compound 43 (Scheme 7). Compound **43** was prepared as described above for compound **18** from compound **33** (9.32 g, 20.0 mmol) in 35 mL of DMSO and compound **38** (3.84 g, 20 mmol). The reaction gave 70-80% yield of compound **43.**

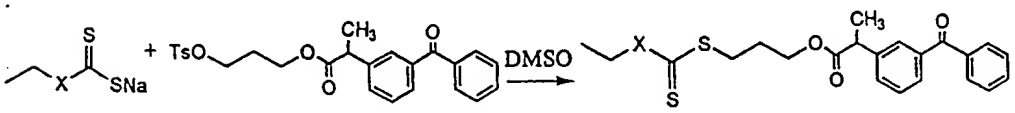
11E. Compound 44 (Scheme 7). Compound **44** was prepared as described above for compound **18** from compound **33** (9.32 g, 20.0 mmol) in 35 mL of DMSO and compound **39** (3.32 g, 20 mmol). The reaction gave 70-80% yield of compound **44.**

EXAMPLE 12

Additional Synthesis of Ketoprofen Conjugates.

The ketoprofen derivatives described in this example are illustrated in Scheme 8.

SCHEME 8



45. X = O
46. X = S

33

47. X = O
48. X = S

12A. Compound 47 (Scheme 8). Compound **47** was prepared as described above for compound **18** from compound **33** (9.32 g, 20.0 mmol) in 35 mL of DMSO and compound **45** (2.88 g, 20 mmol). The reaction gave 70-80% yield of compound **47**.

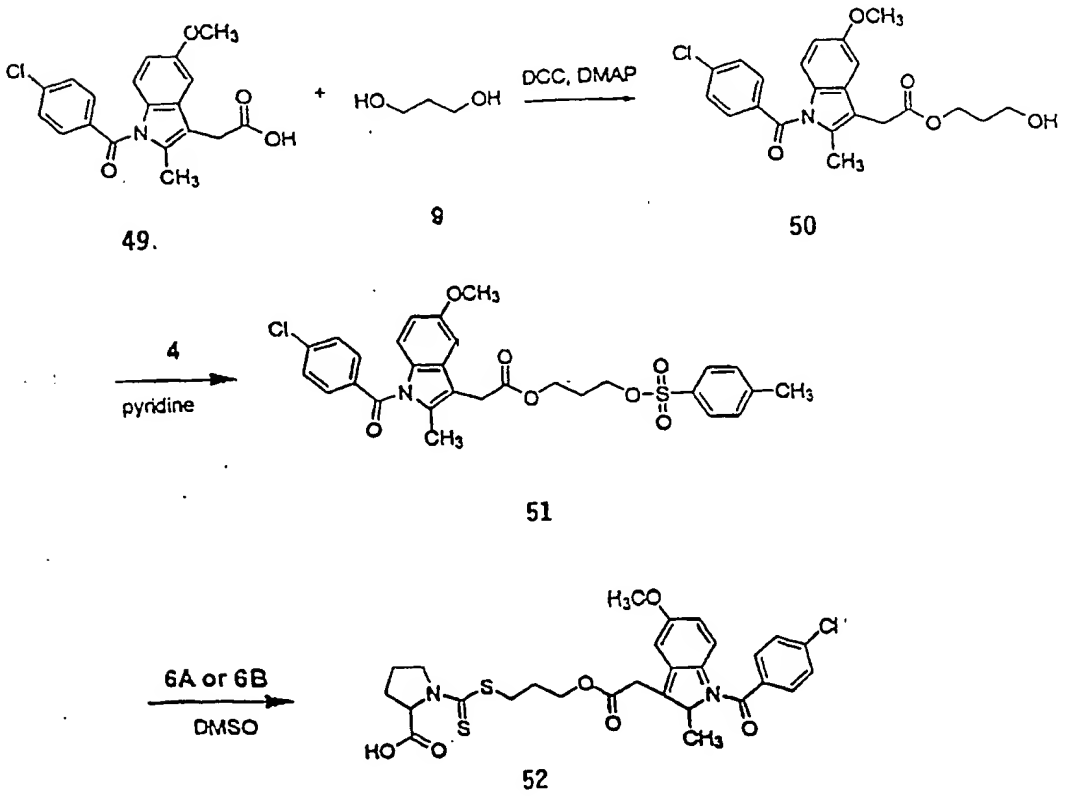
12B. Compound 48 (Scheme 8). Compound **48** was prepared as described above for compound **18** from compound **33** (9.32 g, 20.0 mmol) in 35 mL of DMSO and compound **46** (3.20 g, 20 mmol). The reaction gave 70-80% yield of compound **48**.

EXAMPLE 13

Synthesis of Invention Conjugate of Indomethacin.

The systhetic steps described in this example are illustrated in Scheme 9:

SCHEME 9



49 9 50

51

52

13A. 3-Hydroxypropyl 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate 50 (Scheme 9). Compound **50** is prepared as described above for compound **10** from 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid (indomethacin, **49**) (1.8 g, 5.0 mmol) and propanediol (**9**) (1.9 g, 25 mmol). The compound is purified by flash chromatography on a silica gel column using 200:1, 100:1 and 50:1 CH_2Cl_2-MeOH as eluents to give 1.02 g (49%) of the compound **50** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.70 (t, 1H, ex D_2O), 1.86 (m, 2H), 2.39 (s, 3H), 3.63 (q, 2H), 3.68 (s, 2H), 3.84 (s, 3H), 4.27 (t, 2H), 6.67 (d, 1H), 6.86 (d, 1H), 6.95 (d, 1H), 7.48 (d, 2H), 7.66 (d, 2H); MS (ES) *m/z* 416.5 $(M + H)^+$ ($C_{22}H_{23}ClNO_5$ requires 416.87).

13B. 3-Tosylpropyl 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate 51 (Scheme 9). Compound **51** is prepared as described above for compound **11** from compound **50** (0.96 g, 2.3 mmol) and compound **9** (0.88 g, 4.6 mmol). The compound is purified by flash chromatography on a silica gel column using 3:1 hexanes-ethyl acetate as the eluent to give 0.93 g (71%) of the compound **51** as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.98 (m, 2H), 3.62 (s, 2H), 3.82 (s, 3H), 4.05 (t, 2H), 4.14 (t, 2H), 6.67 (d, 1H), 6.90 (d, 1H), 6.93 (d, 1H), 7.32 (d, 2H), 7.47 (d, 2H), 7.66 (d, 2H), 7.74 (d, 2H); MS (ES) *m/z* 592.0 $(M + Na)^+$ ($C_{29}H_{28}ClNO_7SNa$ requires 592.13).

13C. Compound 52 (Scheme 9). Compound **52** was prepared as described above for compound **12** from compound **51** (0.89 g, 1.56 mmol) and compound **6A** (0.33 g, 0.78 mmol) **or 6B** (0.37g, 1.56 mmol). The compound is purified by flash chromatography on a silica gel column using 200:1 and then 20:1 CH_2Cl_2-MeOH as eluents to give 0.33 g (36%) of the compound **52** as a white foam; ^{1}H NMR ($CDCl_3$) δ 2.01-2.30 (m, 6H), 2.38 (s, 3H), 3.29 (t, 2H), 3.68 (m, 4H), 3.84 (s, 3H), 4.19 (t, 2H), 5.13 (t, 1H), 6.66 (m, 1H), 6.87 (d, 1H), 6.96 (d, 1H), 7.46 (d, 2H), 7.66 (d, 2H); MS (ES) *m/z* 1177.5 $(M + H)^+$ ($C_{54}H_{53}Cl_2N_4O_{12}S_4$ requires 1177.2).

EXAMPLE 14

Enzymatic Hydrolysis of Invention Conjugates.

14A. Enzymatic hydrolysis of compound 12. Compound 12 (4.6 mg, 0.0049 mmol) was dissolved in 0.25 ml of DMSO to make a 0.02M solution. The above solution (0.05 mL) was transferred to 1 mL of PBS buffer and mixed with 33.3 units of the esterase. The resulting solution was put in a water bath (37°C) for 30 min and then at rt overnight. The compound was decomposed into two compounds; Silica gel TLC R_f 0.46 (naproxen) and R_f 0.12 (20:1 CH_2Cl_2-MeOH).

14B. Enzymatic hydrolysis of compound 30. Compound 30 was hydrolyzed as described above for compound **12**. The compound **30** was decomposed into two compounds within 5 h; Silica gel TLC R_f 0.64 (ibuprofen) and R_f 0.12 (20:1 CH_2Cl_2-MeOH).

14C. Enzymatic hydrolysis of compound 34. Compound **34** was hydrolyzed as described above for compound **12**. The compound **34** was decomposed into two compounds within 5 h; Silica gel TLC R_f 0.45 (ketoprofen) and R_f 0.12 (20:1 CH_2Cl_2-MeOH).

14D. Enzymatic hydrolysis of compound 52. Compound **52** was hydrolyzed as described above for compound **12**. The compound **52** was decomposed into two compounds within 5 h; Silica gel TLC R_f 0.44 (indomethacin) and R_f 0.12 (20:1 CH_2Cl_2-MeOH).

EXAMPLE 15

Evaluation of the effects of the conjugate of pyrrolidinol dithiocarbamate and ibuprofen (PDI) on the acute gastric mucosal injury.

Wistar rats (200-250 grams, male) are fasted overnight but allowed free access to water. Ten rats in each group are given ibuprofen or PDI orally at doses of 10, 20 or 50 mg/kg. The rats are sacrificed five hours later and visible gastric damage is assessed by examining under microscope and histological evaluation.

EXAMPLE 16

Evaluation of the effects of the conjugate of pyrrolidinol dithiocarbamate and ibuprofen (PDI) on chronic gastric ulcer.

White New Zealand rabbits (male, about 1 kg) are given subcutaneously ibuprofen or PDI at a dose of 30 mg/kg for every 12 hours. The animals are sacrificed on day 4 (after the 7th dose) and the visible ulcers in the stomach are examined and measured with calipers. The tissue samples are fixed in neutral buffered formalin and processed for histological evaluation.

EXAMPLE 17

Evaluation on the anti-inflammatory effects of the conjugate of pyrrolidinol dithiocarbamate and ibuprofen (PDI).

Wistar rats (male, 200-250 g) are fasted overnight but allowed to free access to drinking water. Ibuprofen or PDI is given orally at a dose of 1, 10, or 30 mg/kg (6 animals each group). After one hour, the rats are anesthetized and 0.1 ml of lambda carrageenan (0.1% solution) is injected into the right hind foot pad. The volume of the pad is measured by hydroplethysmometry every hour for the next five hours.

EXAMPLE 18

Evaluation of the effects of the conjugate of pyrrolidinol dithiocarbamate and ibuprofen (PDI) on prostaglandin synthesis.

Wistar rats (male, 200-250 g) are fasted overnight but allowed free access to drinking water. The rats are anesthetized and their backs are shaved. After an incision to the back, a sponge (2.5 x 1 x 0.5 cm) soaked with 2 ml of 0.5% carrageenan is implanted. Five hours later, the rats (6 animals in each group) are given orally either ibuprofen or PDI at a dose of 30 mg/kg or vehicle control. One hour later, the rat is sacrificed and the sponge is carefully removed. The exudate is recovered from the sponge and the prostaglandin E2 level in the exudate is measured by enzyme-linked immunosorbent assay.

EXAMPLE 19

Evaluation on the protective effects of the conjugate of L-proline dithiocarbamate and adriamycin (PDA) against adriamycin-induced cardiotoxicity.

Balb/c mice (male, 20-25 g) are fed a standard diet and allowed free access to drinking water. The mice are anesthetized and the telemetry system consisting of implantable transmitters, a telemetry receiver and analog ECG adapter is implanted in the peritoneal cavity of each mouse. After surgery, the mice are allowed to recover for two weeks. The mice are given intravenously either adriamycin or PDA at a dose of 4 mg/kg through the tail vein. The treated mice are observed for two weeks. The body weight, ECG and heart rate are recorded daily. At the end of the study, the animals are sacrificed and the hearts are processed for histological evaluation.

EXAMPLE 20

Reduced numbers of gastric erosions in the rat gastropathy model by Naproxen-derived conjugate of the invention.

The main side effect of NSAIDs is gastrointestinal ulceration and intolerance. Gastric damage from orally dosed NSAIDs has both local erosive and systemic ulcerative components. The ability to cause local erosions can be estimated by using the rat gastropathy model (Brand, SJ et al. supra). Sprague-Dawley rats (male, 175-250 g), were food fasted overnight and then dosed orally with 5 to 10 ml/kg of drug, followed by removal of drinking water. After 2.5 hours, the rats were injected i.v. with Evans Blue to stain the gastric erosions. Thirty minutes later the animals were sacrificed by CO_2 inhalation and the stomachs removed, opened along the greater curvature, and washed with water. The total number of blue lesions was counted and the length of the lesions noted.

Administration of Naproxen at 15 and 30 mg/kg and equimolar doses of Naproxen – containing conjugate of the invention (27 & 54 mg/kg) resulted in a dose-related number of lesions for both compounds (Figure 1). Most of the lesions were linear or oval in shape and less than 2 mm in length; they were found primarily in the corpus of the stomach. The group subjected to high dose of the Naproxen – containing conjugate of the invention had significantly fewer lesions than the high dose naproxen group (ANOVA; $p < 0.005$). The group subjected to low dose Naproxen – containing conjugate of the invention also showed fewer erosions than the low dose of naproxen, but statistical significance was not achieved with only 6 animals in each group. These results suggest that the naproxen prodrug, i.e., Naproxen – containing conjugate of the invention, has the ability to reduce the number of erosions in the corpus of the stomach after oral administration in the rat.

EXAMPLE 21

Reduction of acute hindlimb inflammation in the rat carrageenan-induced hindlimb edema model by Naproxen containing conjugates of the invention.

Efficacy of NSAIDs in acute inflammation can be estimated by using intraplantar injection of carrageenan in the rat. Male Sprague-Dawley rats (200-250 g) were injected intradermally in the footpad with 50 µl of a 1% carrageenan solution in PBS. Swelling of the injected paw was measured at 2, 3, 5 & 7 hours using a plethysmometer.

Pretreatment with oral naproxen given one hour before the carrageenan injection at 10 mg/kg resulted in a significant reduction in swelling that lasted from 2 to 5 hours post injection.(Figure 2). An equimolar dose of Naproxen – containing conjugate of the invention (18 mg/kg) reduced inflammation significantly at 2 and 3 hours, but started to wear off by 5 hours. These results suggest that Naproxen – containing conjugate of the invention is orally active in rats, but slightly less effective vs acute inflammation than the parent drug.

Conclusions: Oral Naproxen – containing conjugates according to the invention have antiinflammatory activity similar to naproxen in the chronic adjuvant arthritis and acute carrageenan hindlimb edema rat models. The tendency to cause gastric erosions is reduced in Naproxen – containing conjugates according to the invention. Thus, Naproxen – containing conjugates according to the invention may be effective prodrug form of naproxen with reduced gastric side effects.

EXAMPLE 22

Reduction of chronic hindlimb inflammation in the rat adjuvant arthritis model by Naproxen – containing conjugates of the invention.

NSAIDs are useful in both chronic and acute inflammatory conditions. Efficacy in chronic inflammation can be estimated using the rat adjuvant arthritis model (Blackham et al. supra). In this model Lewis male rats (175-250 g) were injected intradermally in the footpad with M. tuberculosis powder suspended in mineral oil at 5 mg/ml. Progressive swelling of the uninjected paw and ankle joint between days 11 and 15 was measured by plethysmometry.

Rats were dosed daily by by oral gavage with 5 ml/kg of naproxen at 1 and 10 mg/kg and equimolar doses of Naproxen – containing conjugate of the invention (1.8 and 18 mg/kg) on days 5-8 and 11-14. The high doses of both drugs produced a comparable reduction of swelling on days 13 through 15 (Figure 3), with a reduction compared to control of approximately 70% by day 15. The lower doses also appeared to have a slight effect by day 15. The results show that equimolar doses of Naproxen – containing conjugate of the invention resulted in antiinflammatory effects equal to those of naproxen in this model.

EXAMPLE 23

Pharmacokinetics of naproxen in plasma following intravenous administration of naproxen in rats or naproxen – containing conjugates of the invention.

Naproxen is a nonsteroidal anti-inflammatory drug (NSAID) that is widely used in the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendinitis and bursitis, and acute gout. Naproxen sodium, the sodium salt of naproxen, has also been developed as an analgesic because it is more

rapidly absorbed. The side effects of GI ulceration, bleeding, and perforation is problematic to naproxen and NSAID therapy in general. Therefore, any therapeutic approach that decreases the side effects of naproxen could widen the usage of this therapy in treating inflammatory diseases.

The test articles utilized were Naproxen – containing conjugates of the invention (Medinox, Inc., San Diego) stored as a powder (at 4°C) and naproxen (Sigma, St. Louis) stored at room temperature. On the day of animal dosing, test articles were freshly prepared in the mixture of carboxymethylcellulose (Sigma, St. Louis) and dimethylsulfoxide (Sigma, St. Louis) or water for injection.

Rats were catheterized using the carotid artery and jugular vein. The catheters were flushed with 30% polyvinylpyrrolidone (400 U/mL of heparin) to prevent clotting in the tip. 250 μL blood samples were collected by unhooking the flush syringe and letting the blood flow freely into centrifuge tubes at predetermined time points (see **Table 1**). The tubes were centrifuged at 13,000 rpm for 10 min at 4°C. All plasma samples were analyzed for naproxen content on the same day of collection.

A 50 μL aliquot of plasma sample was mixed with 100 μL of acetonitrile. After vortexing and centrifugation, 100 μL of supernatant was collected and added to 150 μL of 50 mM phosphate buffer (pH 5.0). After vortexing and centrifugation, 25 μL of supernatant was analyzed for naproxen by HPLC using a UV detector.

Pharmacokinetic analysis: The average plasma concentration at each time point was calculated and utilized in a pharmacokinetic analysis. Compartmental or noncompartmental pharmacokinetic analyses were performed using the WinNonlin program to calculate the following parameters: maximum concentration at 2 minutes (C_{max}), time to maximum concentration (T_{max}), area under the curve from zero to the last time point (AUC_{last}), area under the curve from zero to infinite time (AUC_{inf}),

terminal phase half life (Beta-$t_{1/2}$), total plasma clearance (CL), and volume distribution at steady state (V_{ss}).

Table 1: Rat group assignment and doses

Test Article	Group #	Rat #	Dose (mg/kg)	Plasma Sample Time
Naproxen	2	1, 2, 3, & 4	IV (0.55 mg/kg)	5 min, 0.5, 1, 2, 3, 4, 5, 6, 7, & 8 hrs
Naproxen prodrug	1	1, 2, 3, & 4	IV (1 mg/kg)	5 min, 0.5, 1, 2, 3, 4, 5, 6, 7, & 8 hrs

Note that 1 mg of Naproxen prodrug contains 0.55 mg of naproxen.

Figure 4 presents the naproxen plasma concentration-time curves. After IV administration of naproxen, the naproxen plasma concentrations declined with bi-exponential manner (blackened rectangles), while the decline of Naproxen prodrug was monophasic (opened triangles). **Table 2** shows the naproxen pharmacokinetic parameters. Both sets of pharmacokinetic parameters were similar except (5.39 and 1.98 μg/mL for naproxen and Naproxen prodrug administration, respectively). This slow release of naproxen from Naproxen prodrug might be advantageous in helping to reduce naproxen's side effects by slowing the rise of plasma C_{max}. In addition, the results show clearly that when administered intravenously, naproxen is released from Naproxen prodrug and appears in the circulation.

Table 2: Naproxen plasma pharmacokinetic parameters (n=4, pooled data) after IV administration of Naproxen prodrug or naproxen in rats (compartmental analysis)

Drug	Amount	C_{max}	AUC_{all}	AUC_{inf}	$t_{1/2}$	CL	V_{ss}
	(mg/kg)	(μg/mL	(μg*min/mL		(hrs)	(mL/hr*kg)	(L/kg)
Naproxen	0.55	5.39	N/A	14.60	4.36	38	0.22
Naproxen prodrug	1.00	1.98	N/A	12.70	4.44	43	0.28

EXAMPLE 24

Plasma pharmacokinetics of naproxen following oral administration of Naproxen prodrug or naproxen in rats

The cannulated rats were separated into two groups as shown in **Table 3**. After oral gavage, the blood samples were withdrawn in various time points (**Table 3**) for HPLC analysis of naproxen levels.

Table 3: Rat group assignment and doses

Test Article	Group #	Rat #	Dose (mg/kg)	Plasma Sample Time
Naproxen	2	5, 6, 7, & 8	oral (2.2 mg/kg)	0.25, 0.5, 1, 3, 5, 7, 9, 11, 13 & 14 hrs
Naproxen prodrug	1	1, 2, 3, & 4	oral (4 mg/kg)	0.25, 0.5, 1, 3, 5, 7, 9, 11, 13 & 14 hrs

Note that 4 mg of the Naproxen prodrug contains 2.2 mg of naproxen.

Figure 5 presents the naproxen plasma concentration-time curves (after oral administration of naproxin (open triangles) and naproxen prodrug (blackened rectangles). Following oral administration of Naproxen prodrug, the time to maximum naproxen plasma levels was considerably delayed compared to naproxen (T_{max} of 1.3 and 6.4 hours for Naproxen prodrug and naproxen, respectively) (**Table 4**). The corresponding C_{max} values were 2.34 and 4.05 aμg/mL, respectively. There was no significant difference for AUC_{inf} values. The lower C_{max}, longer T_{max}, and similar AUC_{inf} of Naproxen prodrug could be significant factors in reducing the side effects of naproxen.

Table 4: Naproxen plasma pharmacokinetic parameters (n=4, pooled data) after oral administration of Naproxen prodrug or naproxen in rats (compartmental analysis)

Drug	Dose	C_{max}	T_{max}	AUC_{all}	AUC_{inf}	$t_{1/2}$
	(mg/kg)	(μg/mL)	(hrs)	(μg*hr/mL)		(hrs)
Naproxen	2.2	4.82	1.3	N/A	48.4	6.0
Naproxen prodrug	4	2.34	6.4	N/A	45.6	7.5

Based on plasma data, Naproxen prodrug by oral or IV administration, produces better naproxen pharmacokinetic profiles than naproxen itself.

While the invention has been described in detail with reference to certain preferred embodiments thereof, it will be understood that modifications and variations are within the spirit and scope of that which is described and claimed.

That which is claimed is:

1. A chemically modified pharmacologically active agent having the structure:

Z-C(S)-S-L-Q

wherein:

Q = a pharmacologically active agent,

L= a linker/spacer, and

Z = a modifying group.

2. A chemically modified pharmacologically active agent according to claim 1 wherein said pharmacologically active agent is selected from NSAIDs, analgesics/antipyretics, sedatives/hypnotics, antianginal agents, antianxiety agents, antidepressants, antipsychotic agents, antimanic agents, antiarrhythmics, antihypertensive drugs, antihistamine/antipruritic drugs, immunosuppressants, antimetabolite cytotoxics, neuroprotective agents, T cell inhibitors, antimigraine agents, antiarthritic agents, antigout agents, anticoagulants, thrombolytic agents, antifibrinolytic agents, hemorheologic agents, antiplatelet agents, anticonvulsants, agents useful for calcium regulation, antibacterial agents, antifungal agents, antiviral agents, antimicrobials, anti-infectives, bronchodialators, hormones, hypoglycemic agents, hypolipidemic agents, proteins, nucleic acids, agents useful for erythropoiesis stimulation, antiulcer/antireflux agents, antinauseants/antiemetics, septic shock agents, multiple sclerosis agents, organ transplantation agents, systemic lupus erythematosus (SLE) agents, Alzheimer's disease agents, antiparkinson agents, psoriasis agents, diabetes agents, stroke agents, agents useful for the treatment of carcinomas, agents useful for the treatment of endometriosis, agents useful for the treatment of uterine contraction, agents useful for the treatment of diuresis, agents useful for the treatment of

cystic fibrosis, agents useful for the treatment of neutropenia, agents useful for the treatment of lung cancer, agents useful for the treatment of respiratory disorders, agents useful for the treatment of ischemia/reperfusion injury, agents useful for the treatment of ophthalmic diseases, agents useful for the treatment of cardiovascular diseases, anti-inflammatory agents or antioxidants.

3. A chemically modified pharmacologically active agent according to claim 1 wherein said pharmacologically active agent is a non-steroidal antiflammatory drug, an antihypertensive agent, an antineoplastic agent, an anti-allograft rejection agent, a neuroprotective agent, an immunosuppressive agent or an antioxidant.

4. A chemically modified pharmacologically active agent according to claim 1 wherein said pharmacologically active agent is aspirin, ibuprofen, ketoprofen, naproxen, diclofenac, adriamycin, cyclosporin, FK506, LFA-1, selectin inhibitors, tissue plasminogen activator or lubeluzole.

5. A chemically modified pharacologically active agent according to claim 1 wherein said modified agent is prepared by reaction of a dithiocarbamate with said pharmacologically active agent.

6. A chemically modified pharacologically active agent according to claim 5 wherein said dithiocarbamate moiety is sarcosine dithiocarbamate, iminodiacetic acid dithiocarbamate, diethyldithiocarbamate, diisopropyldithiocarbamate, sugar-linked dithiocarbamates, pyrrolidine dithiocarbamate or proline dithiocarbamate.

7. A chemically modified pharacologically active agent according to claim 1 wherein the linkage between said pharmacologically active agent and the -S-C(S)- moiety is selected from the group consisting of ester linkages, disulfide linkages, amide linkages, ether linkages, thioether linkages, imide linkages, sulfate ester linkages, sulfonate ester linkages, phosphate ester linkages, carbonate linkages, O-glycosidic linkages and S-glycosidic linkages.

8. A chemically modified pharacologically active agent according to claim 7 wherein said linkage is an ester linkage.

9. A chemically modified pharacologically active agent according to claim 7 wherein said linkage is a disulfide linkage.

10. A chemically modified pharacologically active agent according to claim 7 wherein said linkage is an amide linkage.

11. A chemically modified pharacologically active agent according to claim 7 wherein said linkage is a sulfonate ester linkage.

12. A chemically modified pharacologically active agent according to claim 7 wherein said linkage is a sulfate ester linkage.

13. A chemically modified pharacologically active agent according to claim 7 wherein said linkage is a phosphate ester linkage.

14. A chemically modified pharmacologically active agent according to claim 1 wherein L has the structure:

-Y-W-,

wherein:

Y is alkylene, substituted alkylene, cycloalkylene, substituted cycloalkylene, heterocyclic, substituted heterocyclic, oxyalkylene, substituted oxyalkylene, alkenylene, substituted alkenylene, arylene, substituted arylene, alkarylene, substituted alkarylene, aralkylene or substituted aralkylene, and

W=O, N, P or S.

15. A chemically modified pharmacologically active agent according to claim 1 wherein said modifying group is:

$-CR_3$, $-SiR_3$,

$-NR'_2$, $-PR'_2$,

$-OR''$, $-SR''$,

wherein:

each R is independently alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, acyl, substituted acyl, hydroxy, alkoxy, or substituted alkoxy;

each R' is independently alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, acyl, substituted acyl, hydroxy, alkoxy, or substituted alkoxy; and

R" is alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocyclic, substituted heterocyclic, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkylaryl, substituted alkylaryl, arylalkyl, substituted arylalkyl, arylalkenyl, substituted arylalkenyl, arylalkynyl, substituted arylalkynyl, aroyl, substituted aroyl, acyl or substituted acyl.

16. A chemically modified pharmacologically active agent according to claim 1 in a pharmaceutically acceptable carrier therefor.

17. A chemically modified pharacologically active agent according to claim 16 wherein said pharmaceutically acceptable carrier is selected from a solid, solution, emulsion, dispersion, micelle or liposome.

18. A chemically modified pharacologically active agent according to claim 16 wherein said further comprises an enteric coating.

19. In the administration of a pharmacologically active agent to a subject for the treatment of a pathological condition, the improvement comprising covalently attaching a dithiocarbamate to said pharmacologically active agent prior to administration of said pharmacologically active agent to said subject.

20. In the treatment of a subject suffering from a pathological condition by administration thereto of a pharmacologically active agent, the improvement comprising covalently attaching a dithiocarbamate to said pharmacologically active agent prior to administration thereof to said subject.

21. A method for the treatment of a subject afflicted with a pathological condition, said method comprising administering to said subject an effective amount of a modified pharmacologically active agent,

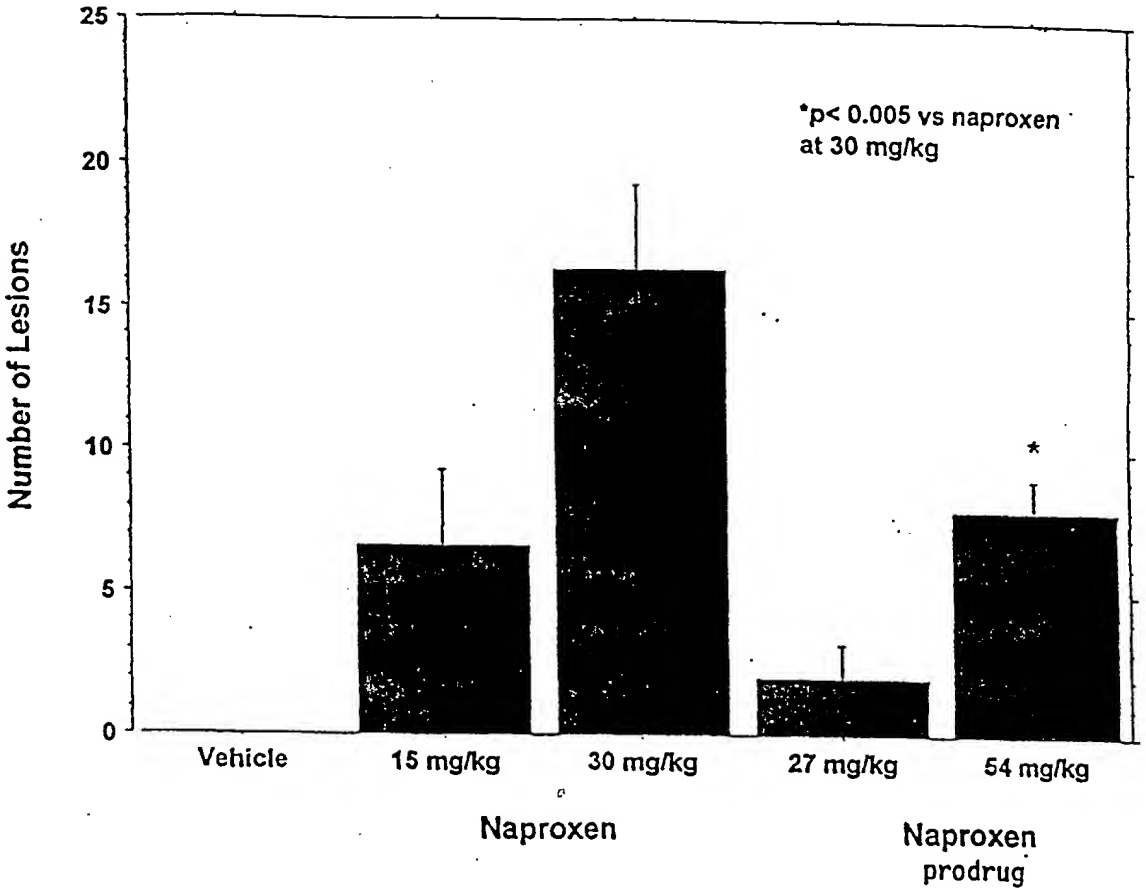
wherein said pharmacologically active agent is effective for treatment of said condition, and

wherein said pharmacologically active agent has been modified by the covalent attachment thereto of a dithiocarbamate.

22. A method for the preparation of a protected form of a pharmacologically active agent, said method comprising covalently attaching a dithiocarbamate to said pharmacologically active agent.

23. A method for reducing the side effects induced by administration of a pharmacologically active agent to a subject, said method comprising covalently attaching a dithiocarbamate to said pharmacologically active agent prior to administration to said subject.

24. A method for enhancing the effectiveness of a pharmacologically active agent, said method comprising covalently attaching a dithiocarbamate to said pharmacologically active agent.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20
15
10
5
0
Number of Lesions
*p< 0.005 vs naproxen at 30 mg/kg
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30 mg/kg
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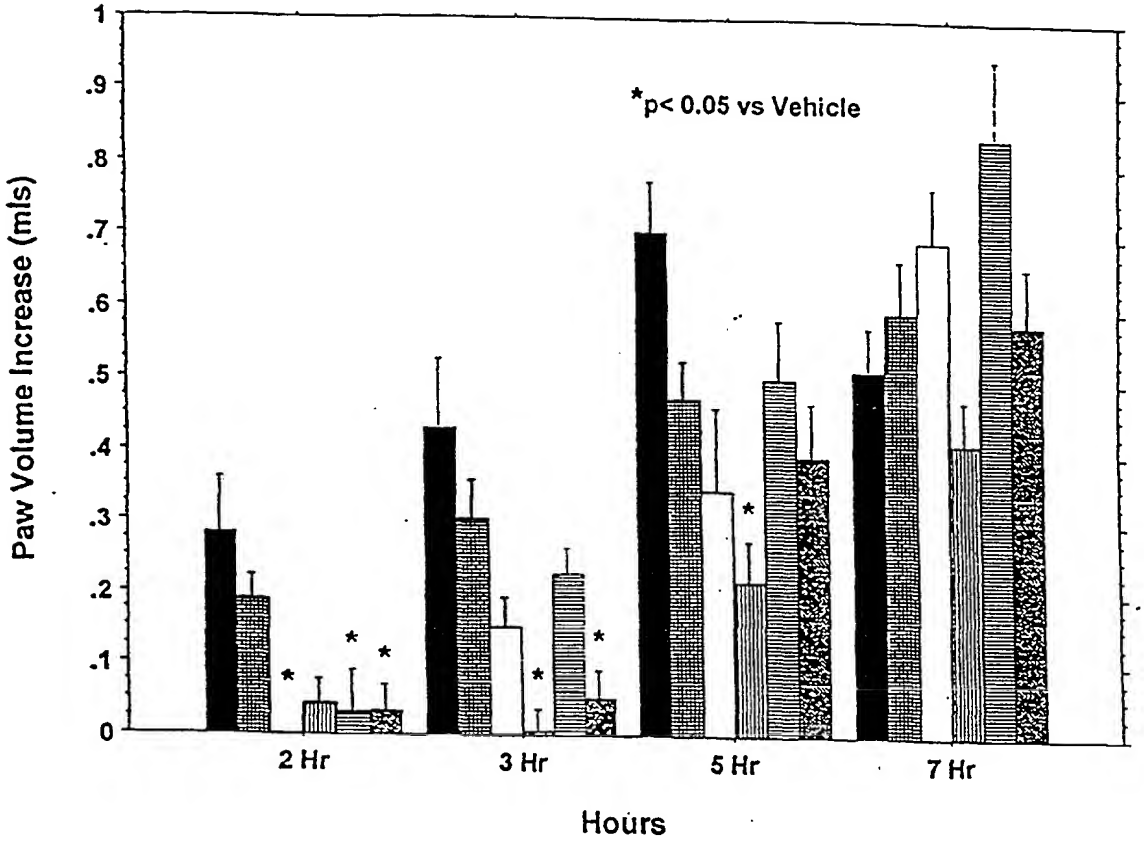
54 mg/kg
Naproxen
Naproxen prodrug

Figure 1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.8
.7
.6
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*p< 0.05 vs Vehicle
2 Hr
3 Hr
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7 Hr
Hours

Figure 2

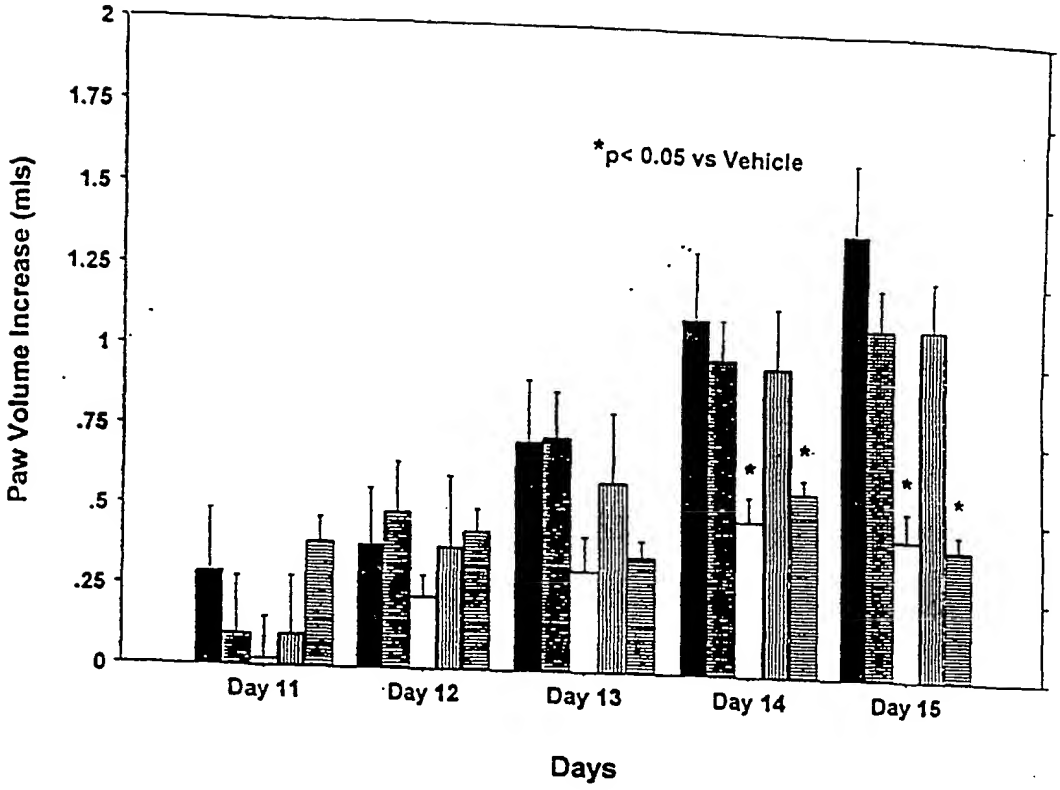
2
1.75
1.5
1.25
1
.75
.5
.25
0
Paw Volume Increase (mls)
*p< 0.05 vs Vehicle
Day 11
Day 12
Day 13
Day 14
Day 15
Days

Figure 3

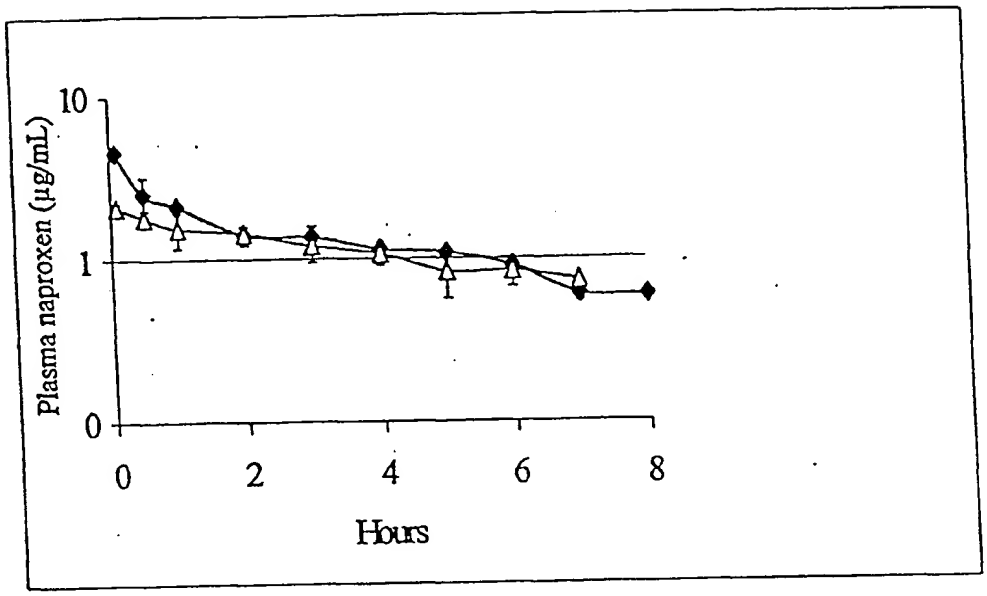

Figure 4

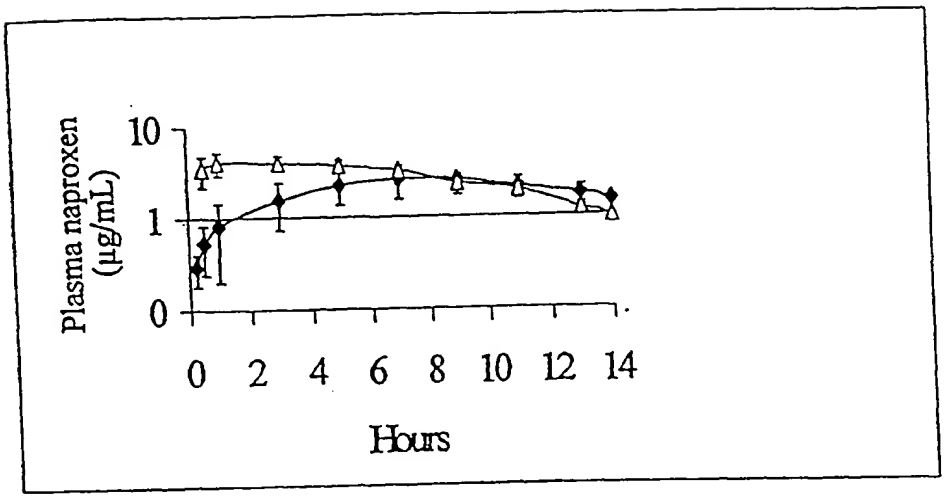

Figure 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/05977

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A01N 37/18
US CL :514/599

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/599, 423

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,807,884 A (MEDFORD et al) 15 September 1998, cols 19-20.	1-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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(54) Title: FATTY ACID-N-SUBSTITUTED INDOL-3-GLYOXYL-AMIDE COMPOSITIONS AND USES THEREOF

(57) Abstract

The present invention pertains to N-substituted indol-3- glyoxyl -amides that are conjugates of fatty acids and N-(pyridin-4-yl) -(1—(4-halobenzyl) -indol-3-yl) -glyoxyl- amides). The conjugates are useful in treating cancer.

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FATTY ACID - N-SUBSTITUTED INDOL-3-GLYOXYL-AMIDE COMPOSITIONS AND USES THEREOF

Field of the invention

The present invention pertains to N-substituted indol-3-glyoxyl-amides that are conjugates of fatty acids and N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amides). The conjugates are useful in treating cancer.

Background of the Invention

Improving drug selectivity for target tissue is an established goal in the medical arts. In general, it is desirable to deliver a drug selectively to its target, so that dosage and, consequently, side effects can be reduced. This is particularly the case for toxic agents such as anti-cancer agents because achieving therapeutic doses effective for treating the cancer is often limited by the toxic side effects of the anti-cancer agent on normal, healthy tissue. The problems relating to lack of drug selectivity can be exemplified by Taxol®(paclitaxel).

Recently, a new class of compounds known as N-substituted indol-3-glyoxyl-amides were synthesized (see PCT WO98/09946, published March 12, 1998). Antiasthmatic, antiallergic and immunosuppressive/immunomodulating properties were associated with these compounds. More recently, investigators from ASTA Medica A.G., Germany (Applicants for the above-identified PCT), reported on the unique anti-cancer properties of one category of these N-substituted indol-3-glyoxyl-amides, namely N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) and N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide) in particular. N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide) appears to be a more potent anti-cancer agent *in vivo* than either taxol or vincristine. Its mechanism of action is believed to involve destabilization of microtubules.

N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide) has attracted strong scientific attention, not only because of its unique antiproliferative potency, but also because it is active against nearly all cancers against which it has been tested.

N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide)'s strength against cancers of diverse tissue origin also represents a significant drawback. An ideal anti cancer agent has tissue specificity, thereby reducing side-effects on normal (dividing) cells. N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide) analogs with tissue specificity therefore are desired. Another drawback of N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide) is its extreme insolubility. N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide) has only been possible to be administered effectively by oral gavage.

Fatty acids previously have been conjugated with drugs to help the drugs as conjugates cross the blood-brain barrier. For example, DHA (docosahexaenoic acid) is a 22 carbon naturally-occurring, unbranched fatty acid that previously has been shown to be unusually effective in crossing the blood-brain barrier. When DHA is conjugated to a drug, the entire drug-DHA conjugate is transported across the blood-brain barrier and into the brain.

DHA is attached via the acid group to hydrophilic drugs and renders these drugs more hydrophobic (lipophilic). DHA is an important constituent of the brain and recently has been approved as an additive to infant formula. It is present in the milk of lactating women. The mechanism of action by which DHA helps drugs conjugated to it cross the blood-brain barrier is unknown.

Another example of the conjugation of fatty acids to a drug is the attachment of pipotiazine to stearic acid, palmitic acid, enanthic acid, undecylenic acid or 2,2-dimethyl-palmitic acid. Pipotiazine is a drug that acts within the central nervous system. The purpose of conjugating pipotiazine to the fatty acids was to create an oily solution of the drug as a liquid implant for slow release of the drug when injected intramuscularly. The release of the drug appeared to depend on the particular fatty acid selected, and the drug was tested for its activity in the central nervous system.

Lipidic molecules, including the fatty acids, also have been conjugated with drugs to render the conjugates more lipophilic than the drug. In general, increased lipophilicity has been suggested as a mechanism for enhancing intestinal uptake of drugs into the lymphatic system, thereby enhancing the entry of the conjugate into the brain and also thereby avoiding first-pass metabolism of the conjugate in the liver. The type of lipidic molecules employed have included phospholipids, non-naturally occurring branched and unbranched fatty acids, and naturally occurring branched and unbranched fatty acids ranging from as few as 8 carbon atoms to more than 30 carbon atoms. In one instance, enhanced receptor binding activity was observed (for an adenosine receptor *agonist*), and it was postulated that the pendant lipid molecule interacted with the phospholipid membrane to act as a distal anchor for the receptor ligand in the membrane micro environment of the receptor. This increase in potency, however, was not observed when the same lipid derivatives of adenosine receptor *antagonists* were used, and generalizations thus were not made possible by those studies.

Summary of the Invention

The present invention involves the unexpected finding that conjugates of a fatty acid and a N-substituted indol-3-glyoxyl-amide, have a different *selectivity* relative to N-

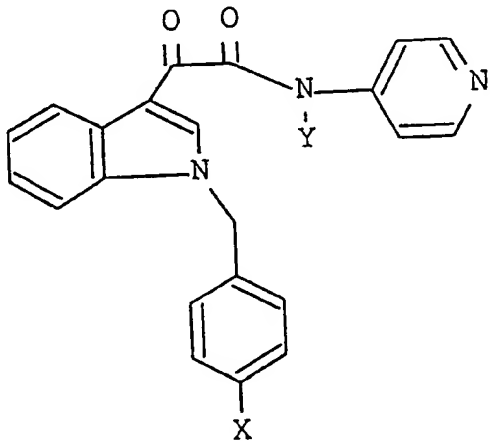
substituted indol-3-glyoxyl-amide alone. The conjugates, in general, render the activity of N-substituted indol-3-glyoxyl-amide selective for biliary tract cancer, brain cancer (including glioblastomas and medulloblastomas), breast cancer; cervical cancer; choriocarcinoma, colon cancer, endometrial cancer, esophageal cancer, gastric cancer, hematological neoplasms, including acute lymphocytic and myelogenous leukemia, multiple myeloma, AIDS associated leukemias and adult T-cell leukemia lymphoma, intraepithelial neoplasms, including Bowen's disease and Paget's disease, liver cancer, lung cancer, lymphomas, including Hodgkin's disease and lymphocytic lymphomas, neuroblastomas, oral cancer, including squamous cell carcinoma, ovarian cancer, including those arising from epithelial cells, stromal cells, germ cells and mesenchymal cells, pancreatic cancer, prostate cancer, rectal cancer, sarcomas, including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibrosarcoma and osteosarcoma, skin cancer, including melanoma, Kaposi's sarcoma, basocellular cancer and squamous cell cancer, testicular cancer, including germinal tumors (seminoma, non-seminoma[teratomas, choriocarcinomas]), stromal tumors and germ cell tumors, thyroid cancer, including thyroid adenocarcinoma and medullar carcinoma, and renal cancer including adenocarcinoma and Wilms tumor ("targeted cancers"). The conjugates, also unexpectedly, restrict the activity of the N-substituted indol-3-glyoxyl-amide even within these foregoing categories of cancer relative to that of N-substituted indol-3-glyoxyl-amide. The conjugates, further unexpectedly, reduce sharply the activity of a N-substituted indol-3-glyoxyl-amide relative to that of N-substituted indol-3-glyoxyl-amide in most cell lines of various tissue types, it is believed, *other than* bone, bone marrow, brain, breast, central nervous system, cervix, colon, endometrium, esophagus, gall bladder, intraepithelium, kidney, liver, lung, ovaries, pancreas, prostate, rectum, skin, squamous cell epithelium, stomach, testicular tissue, and thyroid, thereby reducing potential side effects of the conjugates versus those of N-substituted indol-3-glyoxyl-amide. The therapeutic index of the conjugates is improved, versus that of N-substituted indol-3-glyoxyl-amide for targeted cancers. A preferred N-substituted indol-3-glyoxyl-amide conjugated to a fatty acid according to the invention, is N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide). A preferred N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) is N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide).

According to one aspect of the invention, novel compounds and pharmaceutical compositions are provided. Each pharmaceutical composition contains the novel compound, which is a covalent conjugate of a N-substituted indol-3-glyoxyl-amide and a fatty acid having 8-26 carbons, in an amount effective to treat cancer, and a pharmaceutically

acceptable carrier. Preferably, the fatty acid is an unbranched, naturally occurring fatty acid. More preferably, the fatty acid has 14-22 carbons. Unbranched common naturally occurring fatty acids include C12:0 (lauric acid), C14:0 (myristic acid), C16:0 (palmitic acid), C16:1 (palmitoleic acid), C16:2, C18:0 (stearic acid), C18:1 (oleic acid), C18:1-7 (vaccenic), C18:2-6 (linoleic acid), C18:3-3 (α-linolenic acid), C18:3-5 (eleostearic), C18:3-6 (_-linolenic acid), C18:4-3, C20:1 (gondoic acid), C20:2-6, C20:3-6 (dihomo-y-linolenic acid), C20:4-3, C20:4-6 (arachidonic acid), C20:5-3 (eicosapentaenoic acid), C22:1 (docosenoic acid), C22:4-6 (docosatetraenoic acid), C22:5-6 (docosapentaenoic acid), C22:5-3 (docosapentaenoic acid), C22:6-3 (docosahexaenoic acid) and C24:1-9 (nervonic). Highly preferred unbranched, naturally occurring fatty acids are those with between 14 and 22 carbon atoms. In some embodiments, the fatty acids are ω-3 fatty acids. The most preferred ω-3 fatty acid is docosahexaenoic acid. In certain embodiments, the fatty acids are ω-6 fatty acids. The most preferred ω-6 fatty acid is linoleic acid. In one embodiment, the N-substituted indol-3-glyoxyl-amides are N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide). In a preferred embodiment, the N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) is N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide).

As used in connection with the following conjugates described below, R is the organic substituent attached to the carboxyl-group in any one of the fatty acids described in the immediately preceding paragraph. The fatty acid, preferably, is an ω-3 fatty acid, and most preferably is DHA. Preferably, the covalent conjugate is selected from the group consisting of:

Conjugate 1

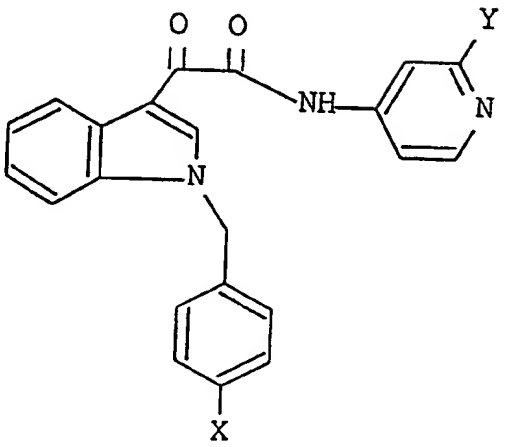


wherein X is H, F, Cl, Br or I;

Y is -COR, -$(CH_2)_nO_2CR$, -$(CH_2)_nNHCOR$, -$CO(CH_2)_nO_2CR$, or

$-CO(CH_2)_nNHCOR$, wherein n=1-22.

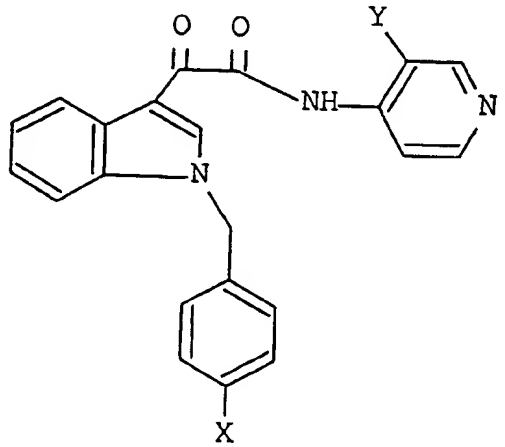
Conjugate 2



wherein X is H, F, Cl, Br or I;

Y is $-O_2CR$, $-NHCOR$, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

Conjugate 3



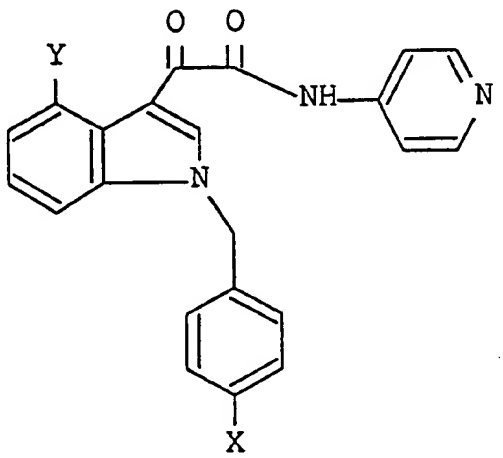
wherein X is H, F, Cl, Br or I;

Y is $-O_2CR$, $-NHCOR$, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$,

$-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$,

$-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

Conjugate 4

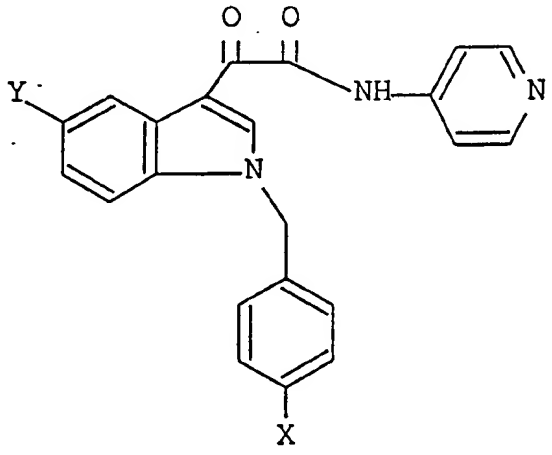


wherein X is H, F, Cl, Br or I;

Y is $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$,

$-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

Conjugate 5



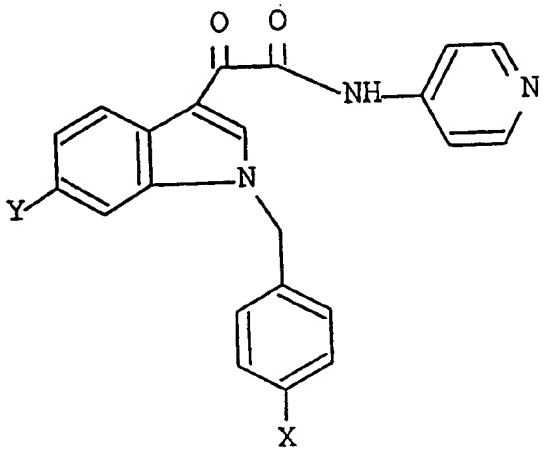
wherein X is H, F, Cl, Br or I;

Y is $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$,

$-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$,

$-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

Conjugate 6

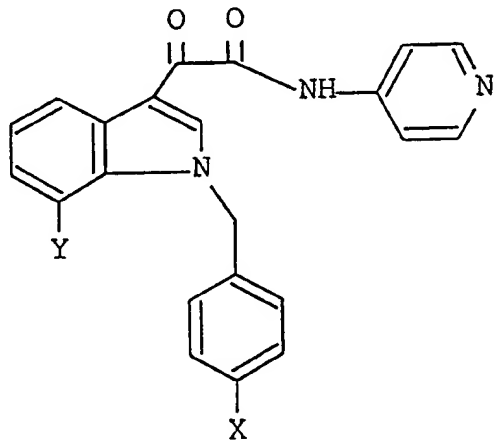


wherein X is H, F, Cl, Br or I;

Y is $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$,

$-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

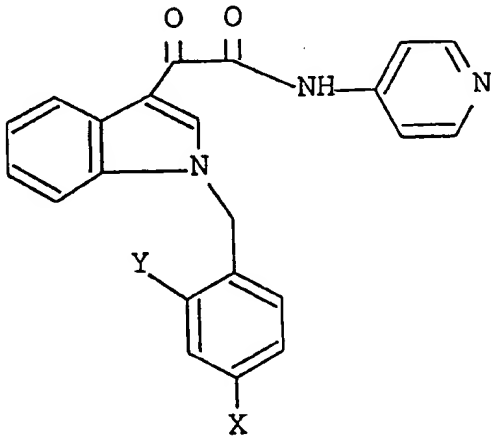
Conjugate 7



wherein X is H, F, Cl, Br or I;

Y is $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

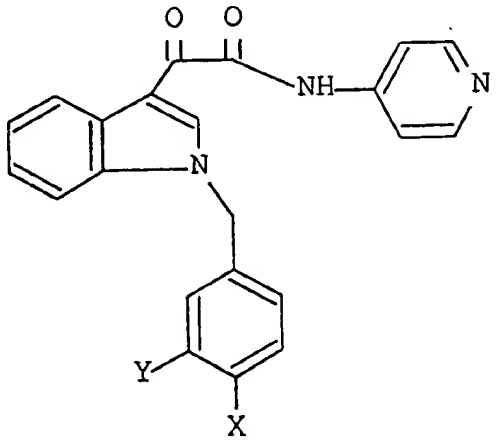
Conjugate 8



wherein X is H, F, Cl, Br or I;

Y is $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

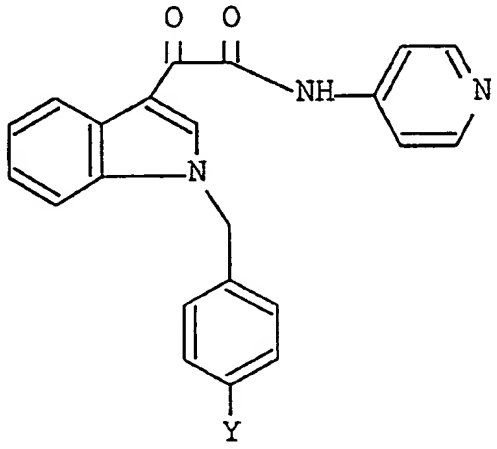
Conjugate 9



wherein X is H, F, Cl, Br or I;

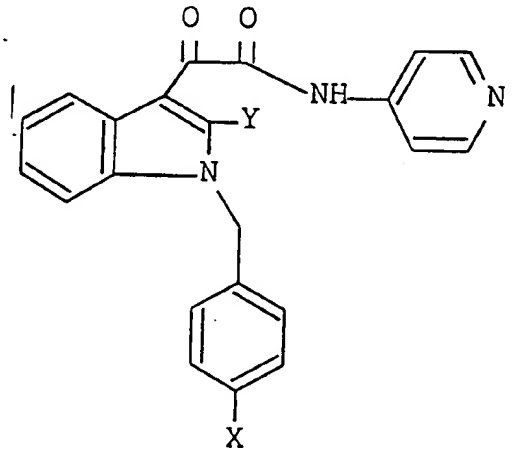
Y is $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

Conjugate 10



wherein Y is $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

Conjugate 11

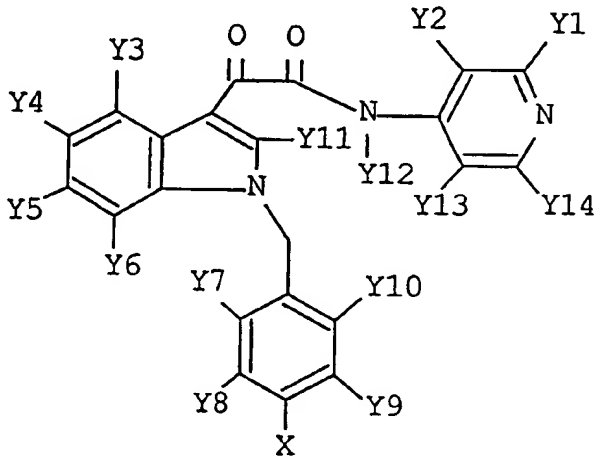


wherein X is H, F, Cl, Br or I;

Y is $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22.

In other embodiments, the covalent conjugate is conjugate 12:

Conjugate 12

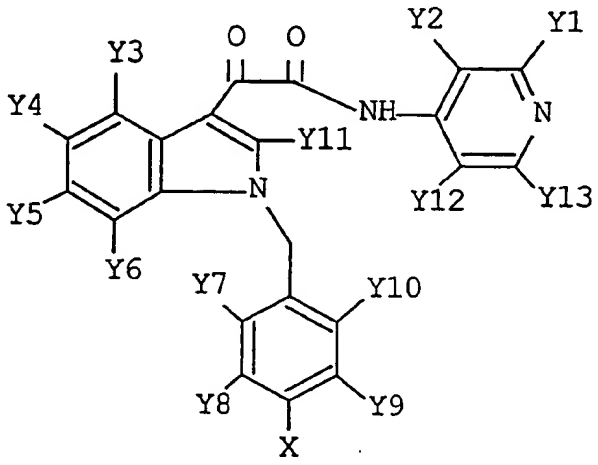


wherein X is F, Cl, Br, I, or Y, wherein Y_1-Y_{14} (collectively Y) is selected from the group consisting of -H,$-O_2CR$,-NHCOR,$-(CH_2)_nO_2CR$,$-(CH_2)_nNHCOR$,$-O_2C(CH_2)_nO_2CR$,$-O_2C(CH_2)_nNHCOR$,$-O(CH_2)_nO_2CR$,$-O(CH_2)_nNHCOR$,-$NHCO(CH_2)_nO_2CR$,-$NHCO(CH_2)_nNHCOR$,$-NH(CH_2)_nO_2CR$,$-NH(CH_2)_nNHCOR$,-COR,$-(CH_2)_nO_2CR$,-$(CH_2)_nNHCOR$, $-CO(CH_2)_nO_2CR$, and $-CO(CH_2)_nNHCOR$, wherein n=1-22, and wherein at least one Y is not Hydrogen (e.g., Y_1) and is selected from the group consisting of $-O_2CR$,-NHCOR,$-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$,$-O_2C(CH_2)_nNHCOR$,-$O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$,$-NHCO(CH_2)_nO_2CR$,$-NHCO(CH_2)_nNHCOR$,-$NH(CH_2)_nO_2CR$,$-NH(CH_2)_nNHCOR$,-COR,$-(CH_2)_nO_2CR$,$-(CH_2)_nNHCOR$,$-CO(CH_2)_nO_2CR$, and $-CO(CH_2)_nNHCOR$, wherein n=1-22, the remainining Y groups (e.g.,Y_2-Y_{14}) can be substituted, or preferably are unsubstituted and are Hydrogens. In further embodiments, in the covalent conjugate 12, at least two, at least three, or at least four Y groups are not Hydrogen and are selected from the group consisting of $-O_2CR$,-NHCOR,$-(CH_2)_nO_2CR$,-$(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$,$-O(CH_2)_nO_2CR$,$-O(CH_2)_nNHCOR$,-

$NHCO(CH_2)_nO_2CR$,-$NHCO(CH_2)_nNHCOR$,-$NH(CH_2)_nO_2CR$,-$NH(CH_2)_nNHCOR$,-COR,-$(CH_2)_nO_2CR$,-$(CH_2)_nNHCOR$,-$CO(CH_2)_nO_2CR$, and -$CO(CH_2)_nNHCOR$, wherein n=1-22, and the remainining Y groups can be substituted, or preferably are unsubstituted and are Hydrogens.

In other embodiments, the covalent conjugate is conjugate 13:

Conjugate 13

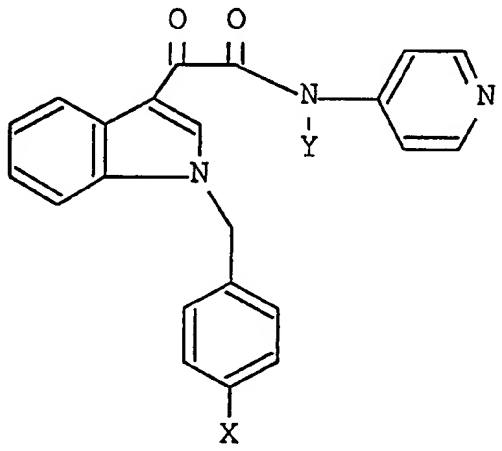


wherein X is F, Cl, Br, I, or Y, wherein Y_1-Y_{13} (collectively Y) is selected from the group consisting of -H, -O_2CR, -NHCOR, -$(CH_2)_nO_2CR$, -$(CH_2)_nNHCOR$, -$O_2C(CH_2)_nO_2CR$, -$O_2C(CH_2)_nNHCOR$, -$O(CH_2)_nO_2CR$, -$O(CH_2)_nNHCOR$, -$NHCO(CH_2)_nO_2CR$, -$NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, -$NH(CH_2)_nNHCOR$, wherein n=1-22, and wherein at least one Y is not Hydrogen (e.g., Y_1) and is selected from the group consisting of -O_2CR, -NHCOR, -$(CH_2)_nO_2CR$, -$(CH_2)_nNHCOR$, -$O_2C(CH_2)_nO_2CR$, -$O_2C(CH_2)_nNHCOR$, -$O(CH_2)_nO_2CR$, -$O(CH_2)_nNHCOR$, -$NHCO(CH_2)_nO_2CR$, -$NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, -$NH(CH_2)_nNHCOR$, wherein n=1-22, the remainining Y groups (e.g.,Y_2-Y_{13}) can be substituted, or preferably are unsubstituted and are Hydrogens. In further embodiments, in the covalent conjugate 13, at least two, at least three, or at least four Y groups are not Hydrogen and are selected from the group consisting of -O_2CR,-NHCOR,-$(CH_2)_nO_2CR$,-$(CH_2)_nNHCOR$, -$O_2C(CH_2)_nO_2CR$, -$O_2C(CH_2)_nNHCOR$,-$O(CH_2)_nO_2CR$,-$O(CH_2)_nNHCOR$,-$NHCO(CH_2)_nO_2CR$,-$NHCO(CH_2)_nNHCOR$,-$NH(CH_2)_nO_2CR$,-$NH(CH_2)_nNHCOR$, wherein n=1-22, and the remainining Y groups can be substituted, or preferably are unsubstituted and are Hydrogens.

In any one of conjugates 12 or 13, when the at least one, the at least two, and/or the at least three Y group(s) is (are) not Hydrogen and is (are) selected from any of the foregoing sub-groups, the remaining Y groups may be also substituted, or preferably are unsubstituted and are Hydrogen substituents. One of ordinary skill in the art could identify other substituent molecules that can be utilized to substitute for the Y group(s), and maintain and/or enhance the conjugate's anti-cancer properties.

In other embodiments, the covalent conjugate is conjugate 14:

Conjugate 14



wherein X is selected from the group consisting of H, F, Cl, Br, I,-O_2CR,-NHCOR,-$(CH_2)_nO_2CR$,-$(CH_2)_nNHCOR$,-$O_2C(CH_2)_nO_2CR$,-$O_2C(CH_2)_nNHCOR$,-$O(CH_2)_nO_2CR$,-$O(CH_2)_nNHCOR$,-$NHCO(CH_2)_nO_2CR$,-$NHCO(CH_2)_nNHCOR$,-$NH(CH_2)_nO_2CR$, and -$NH(CH_2)_nNHCOR$, and Y is selected from the group consisting of -COR, -$(CH_2)_nO_2CR$, -$(CH_2)_nNHCOR$, -$CO(CH_2)_nO_2CR$, and -$CO(CH_2)_nNHCOR$, wherein n=1-22.

Typically the covalent conjugates of the invention include only one fatty acid, although sometimes two, three, four, or more are possible.

According to another aspect of the invention, a kit is provided. The kit is a package which houses a container which contains a covalent conjugate of the invention and also houses instructions for administering the covalent conjugate to a cancer victim.

According to another aspect of the invention, a second kit is provided. This kit includes a package which houses a first container which contains a covalent conjugate of the invention and also houses a second container containing an anti-cancer agent other than the covalent conjugate.

In the kits of the invention, the preferred fatty acids, bonds, covalent conjugate and anti-cancer agent other than the covalent conjugate are as described above.

According to another aspect of the invention, a method is provided for treating cancer. The method involves administering to a subject in need of such treatment a covalent conjugate of an N-substituted Indol-3-glyoxyl-amid and a fatty acid having 8-26 carbons in an amount effective to treat cancer. The preferred N-substituted indol-3-glyoxyl-amid is N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amid). The preferred fatty acids, bonds and covalent conjugates are as described above. The method also can involve co-administering to the subject an anti-cancer agent other than the covalent conjugate. Preferred anti-cancer agents are as described above.

According to one aspect of the invention, a conjugate composition for administration to a subject is provided. The composition includes at least one conjugate in a container for administration to a subject. The amount of the conjugate in the container is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anti cancer compound. Preferably the amount of the conjugate in the container is at least about 20% greater than the MTD, 30% greater than the MTD, 40% greater than the MTD, 50% greater than the MTD, 75% greater than the MTD, 100% greater than the MTD, 200% greater than the MTD, 300% greater than the MTD, or 400% greater than the MTD for the unconjugated at least one anti cancer compound. In certain preferred embodiments, the container is a container for intravenous administration. In certain embodiments, the conjugate is not encapsulated in or in the form of a liposome.

According to still another aspect of the invention, methods for treating a subject having an abnormal mammalian cell proliferative disorder are provided. The methods include administering a composition including at least one fatty acid conjugate to the subject in an amount which is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anti cancer compound. Preferably the amount of the at least one fatty acid-anti cancer compound administered is at least about 20% greater than the MTD, 30% greater than the MTD, 40% greater than the MTD, 50% greater than the MTD, 75% greater than the MTD, 100% greater than the MTD, 200% greater than the MTD, 300% greater than the MTD, or 400% greater than the MTD for the unconjugated at least one anti cancer compound. In certain embodiments the conjugate is not encapsulated in or in the form of a liposome.

In still another aspect of the invention, kits for administration of a fatty acid-anti cancer compound conjugate to a subject is provided. The kits include a container containing a

composition which includes at least one fatty acid-anti cancer compound conjugate of the invention, and instructions for administering the at least one fatty acid-anti cancer compound conjugate to subject in need of such treatment in an amount which is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anti cancer compound. Preferably the subject has an abnormal mammalian cell proliferative disorder. Preferably the amount of the at least one fatty acid-anti cancer compound conjugate to be administered is at least about 20% greater than the MTD, 30% greater than the MTD, 40% greater than the MTD, 50% greater than the MTD, 75% greater than the MTD, 100% greater than the MTD, 200% greater than the MTD, 300% greater than the MTD, or 400% greater than the MTD for the unconjugated at least one anti cancer compound. In certain preferred embodiments, the container is a container for intravenous administration. In certain embodiments the conjugate is not encapsulated in or in the form of a liposome.

A method for increasing the therapeutic index of anti cancer compounds in a subject is provided, according to another aspect of the invention. The method includes conjugating a fatty acid to an anti cancer compound as described herein to form a fatty acid-anti cancer compound conjugate of the invention; and administering the fatty acid-anti cancer compound conjugate to the subject. The therapeutic index of the anti cancer compound thus administered is improved relative to non-conjugated formulations of the anti cancer compound. Preferably the subject has an abnormal mammalian cell proliferative disorder, and the subject preferably is human. In certain embodiments the conjugate is not encapsulated in or in the form of a liposome.

In the foregoing methods, it is preferred that a dose of a fatty acid-conjugated anti-cancer compound is administered which exceeds the maximum tolerated dose of the unconjugated anti cancer compound.

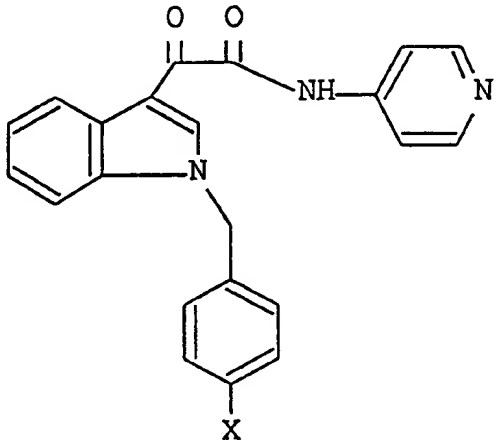
These and other aspects of the invention, as well as various advantages and utilities, will be more apparent with reference to the detailed description of the preferred embodiments.

Brief Description of the Drawings

Figure 1 depicts a kit 11 comprising packaging 15, a first agent of the invention 17 (e.g., a container that contains a fatty acid conjugate of a N-substituted indol-3-glyoxyl-amide, a second agent of the invention 19 (e.g., a container that contains a nonN-substituted indol-3-glyoxyl-amide anticancer agent), and instructions 21, for utilizing such agents in therapeutic applications.

Detailed Description of the Invention

N-substituted indol-3-glyoxyl-amides are synthesized according to PCT WO98/09946, published March 12, 1998, which is expressly incorporated herein by reference. A preferred N-substituted indol-3-glyoxyl-amide according to the invention is N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) has the following structure:



wherein X is a halogen. A preferred N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) is N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide). The preferred source of N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide) is ASTA Medica A.G., Dresden, Germany.

The invention provides compositions of matter. Compositions according to one aspect of the invention comprise a conjugate of a fatty acid and a N-substituted indol-3-glyoxyl-amide. In this aspect of the invention, the fatty acids are polyunsaturated fatty acids. In some embodiments, the fatty acid is preferably a C16-C26 unbranched, naturally occurring fatty acid. The fatty acid can be selected from the group consisting of C8:0 (caprylic acid), C10:0 (capric acid), C12:0 (lauric acid), C14:0 (myristic acid), C16:0 (palmitic acid), C16:1 (palmitoleic acid), C16:2, C18:0 (stearic acid), C18:1 (oleic acid), C18:1-7 (vaccenic), C18:2-6 (linoleic acid), C18:3-3 (α-linolenic acid), C18:3-5 (eleostearic), C18:3-6 (β-linolenic acid), C18:4-3, C20:1 (gondoic acid), C20:2-6, C20:3-6 (dihomo-y-linolenic acid), C20:4-3, C20:4-6 (arachidonic acid), C20:5-3 (eicosapentaenoic acid), C22:1 (docosenoic acid), C22:4-6 (docosatetraenoic acid), C22:5-6 (docosapentaenoic acid), C22:5-3 (docosapentaenoic), C22:6-3 (docosahexaenoic acid) and C24:1-9 (nervonic). Particularly preferred is docosahexaenoic acid. In certain embodiments, the fatty acid can be linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, 2-octanoate, 2-hexanoate, CH_3-hexanoate, CH_3-butanoate, or oleic acid. In particularly preferred

embodiments, the fatty acid is linoleic acid, palmitic acid, arachidonic acid, eicosapentaenoic acid, or docosahexaenoic acid.

cis-docosahexaenoic acid (DHA) is a naturally occurring fatty acid. It is an unbranched chain fatty acid with six double bonds, all *cis*. Its structure is as follows:

DHA can be isolated, for example, from fish oil or can be chemically synthesized. These methods, however, can generate *trans* isomers, which are difficult and expensive to separate and which may present safety problems in humans. The preferred method of production is biological synthesis to produce the all *cis* isomer. The preferred source of DHA is from Martek Biosciences Corporation of Columbia, Maryland. Martek has a patented system for manufacturing DHA using microalgae which synthesize only a single isomer of DHA, the all *cis* isomer. Martek's patents include U.S. Pat. Nos. 5,374,657, 5,492,938, 5,407,957 and 5,397,591.

DHA also is present in the milk of lactating women, and Martek's licensee has obtained approval in Europe of DHA as a nutritional supplement for infant formula.

It is known that DHA can be unstable in the presence of oxygen. To stabilize DHA and its conjugates it is important to add anti-oxidants to the material after it is synthesized. One method of stabilization is to make-up the newly synthesized material in the following solution:

100 g neat DHA-N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide) plus 100 g of vehicle (100ml propylene glycol, 70 mg alpha-tocopherol, 5 mg dialaurylthiodipropionic acid, 50 mg ascorbic acid) prepared and held under argon in amber, sealed vials and stored at four degrees centigrade. The following anti-oxidants may also be employed: ascorbic acid, ascorbyl palmitate, dilauryl ascorbate, hydroquinone, butyated hydroxyanisole, sodium meta bisulfite, *t*-β carotene and α-tocopherol. A heavy metal chelator such as ethylenediamine tetra-acetic acid (EDTA) may also be used.

In one aspect of the invention, the conjugate is prepared as a quaternary ammonium salt. The anion preferably is selected from the group consisting of I^-, Cl^-, OH^-, F^- and Br^-. Most preferably the anion is I^-.

Cancer patients could be evaluated to determine if conjugates 1 -18 are strongly active against the patient's cancer prior to selecting any of the conjugates 1-18 as the anti-cancer agent of choice for that patient.

The foregoing experiments establish that the conjugates of the invention will have altered specificity versus that of the N-substituted indol-3-glyoxyl-amide alone, for cancer cell lines. Because of this altered specificity, it also is clear that the conjugates themselves are gaining access into the target cells (as opposed to simply releasing the N-substituted indol-3-glyoxyl-amide into the environment outside of the cell). Thus, the fatty acid moiety appears to selectively target certain cell types as opposed to others. The ability of the conjugates to gain entry into the targeted cells was unknown prior to the invention, and the ability of the fatty acid moiety to selectively target certain cell types was unexpected.

Paclitaxel was first isolated from the bark of Taxus brevifolia (Wani et al., J. Am. Chem. Soc., 93, 2325, 1971). Its isolation and synthesis have been reported extensively in the literature. Applicants obtained paclitaxel from a commercial source, Hauser Laboratories, of Boulder, Colorado.

The compound of the invention described in Examples 3-9 below, "Taxoprexin™", is a covalent conjugate of DHA and paclitaxel. Its chemical structure, synthesis, purification and *in vitro* action are described in U.S Patne 5,795,909, the entire disclosure of which is incorporated by reference herein. The structure is shown as "conjugate 1" in Example 1 of that patent.

The maximum tolerated dose (MTD) for any therapeutic compound is identified as part of its clinical evaluation. For example, phase I trials can include a determination of the maximum tolerated dose, dose limiting toxicities (DLT) and pharmacokinetics of a test compound. "Maximum tolerated dose," as used herein, refers to the largest dose of a pharmaceutical agent that an adult patient can take with safety to treat a particular disease or condition. Thus, the MTD for any Food and Drug Administration (FDA) approved therapeutic compound is known to those of ordinary skill in the art as a matter of the public record. The MTD for any particular therapeutic compound may vary according to its formulation (e.g., injectable formulation, implantable bioerodible polymer formulation, oral formulation), route of delivery (e.g., intravenous, oral, intratumoral), manner of delivery (e.g., infusion, bolus injection), dosing schedule (e.g., hourly, daily, weekly) and the like. The MTD frequently is defined as the highest dose level at which 50% of subjects administered with the drug develop a dose limiting toxicity. The doses for anti-neoplastic

pharmaceutical agents found in the Physicians Desk Reference (PDR) are defined as the MTD for those agents. The MTD is further defined to include only doses for drugs (including anti-neoplastics) used as single agents and without additional cellular, genetic, pharmaceutical, or other agents added to alter the MTD. Other definitions which are clinically relevant and generally accepted will be known to one of ordinary skill in the art.

Measurement of maximum tolerated dose may be expressed as weight of drug per weight of subject, weight of drug per body surface area, etc. The MTD of anticancer compounds is frequently expressed as weight per square meters (mg/m^2) of body surface area. For example, the MTD for paclitaxel infusion in humans is 225 mg/m^2. The most often used clinical tolerated dose is 175 mg/m^2. MTD also may be expressed as a dose relative to a time component, such as weight of drug per body surface area per day.

For therapeutics which have not yet been subjected to human clinical trails, or subjected to any determination of the MTD in humans (e.g., experimental or highly toxic compounds), one of skill in the art can estimate the MTD by using animal models. Calculation of MTD in animals may be based on a number of physiological parameters, such as death, particular toxicities, drug induced weight loss. Using death as an endpoint, the MTD may be the dose given test animals in which each member of the test group survived. Using toxicity as an endpoint, the MTD may be the dose at which moderate but not severe toxicity is observed. Using weight loss as an endpoint, the MTD may be the dose above which a certain percent change in body weight is induced. Other methods for determining MTDs using animal models and various endpoints are known to one of ordinary skill in the art. Correlation of animal MTDs to human MTDs for a therapeutic compound is an accepted practice in the pharmaceutical arts.

For example, it has been determined that a conjugate of DHA and paclitaxel (Taxoprexin™) has a maximum tolerated dose in animals (mice, rats and dogs) which is about 4-5 times greater (by weight) than paclitaxel alone or about 3-4 times greater (by molarity) than paclitaxel alone.

Thus the invention in another aspect provides compositions and formulations for administration to a subject, preferably a human subject, containing amounts of a fatty acid-anti cancer compound conjugate which exceeds the maximum tolerated dose for the unconjugated anti cancer compound. The fatty acid-anti cancer compound conjugate preferably is in a container for administration to a subject. Preferably the container is a container for intravenous administration, such as an IV bag.

The amount of the fatty acid-anti cancer compound in the container is at least about 10% greater than the MTD for the unconjugated compound. Preferably the amount of the fatty acid-anti cancer compound in the container is at least about 20%, 30%, 40%, 50%, 75%, 100%, 200%, 300% or 400% greater than the MTD for the unconjugated at least one anti cancer compound.

Methods for administering these compositions to subjects having an abnormal mammalian cell proliferative disorder also are provided.

Kits containing fatty acid-anticancer compounds in amounts also are provided. The kits contain one or more containers with the conjugated anticancer compound along with instructions for mixing, diluting and/or administering the anticancer compound in amounts greater than the MTD for the unconjugated anticancer compound. The kits also can include other containers with one or more solvents, surfactants, preservatives and/or diluents (e.g. normal saline (0.9% NaCl), or 5% dextrose (D5W)), as well as containers for mixing, diluting, and/or administering the conjugates to a subject in need of such treatment. A kit embodying features of the present invention, generally designated by the numeral 11, is illustrated in Figure 1. Kit 11 is comprised of the following major elements: packaging 15, a first agent of the invention 17 (e.g., a container that contains a fatty acid conjugate of a N-substituted indol-3-glyoxyl-amide, a second agent of the invention 19 (e.g., a container that contains a nonN-substituted indol-3-glyoxyl-amide anticancer agent), and instructions 21 for utilizing such agents in therapeutic applications. Individuals skilled in the art can readily modify packaging 15 to suit individual needs.

The anti cancer compounds in the kit may be provided as liquid solutions, or as dried powders. When the compound provided is a dry powder, the powder may be reconstituted by the addition of a suitable solvent, which also may be provided. Liquid forms of the conjugates may be concentrated (for dilution prior to administration) or ready to administer to a subject.

As noted above, the therapeutic index is the ratio of the median toxic dose to the median effective dose. Conjugation of fatty acids to anticancer compounds to form a fatty acid-anticancer compound conjugate reduces toxicity of the anticancer compounds, and increases effectiveness as compared to the unconjugated anticancer compounds. Therefore the invention also provides methods for increasing the therapeutic index of anticancer compounds in a subject. The methods include conjugating a fatty acid to an anticancer compound to form a fatty acid-anticancer compound conjugate and administering the fatty acid-anticancer compound conjugate to the subject. The therapeutic index of the anticancer

compound conjugate is improved relative to unconjugated formulations of the anticancer compound. Preferably the anticancer compound is a taxane, particularly paclitaxel or docetaxel.

Although the conjugate may be encapsulated in a liposome, it is preferred that the conjugate is not encapsulated by a liposome. The preferred subjects for the method are humans.

The conjugated anti cancer compounds described herein are less toxic and more effective than the corresponding unconjugated anti cancer compounds. Therefore the fatty acid-anti cancer compound conjugates can be administered in amounts which are equally toxic but more effective, or in doses which are equally effective and less toxic than the corresponding unconjugated anti cancer compounds. In general, conjugation of fatty acids to anti cancer compounds permits an increase in the maximum tolerated dose relative to unconjugated anti cancer compounds.

The compounds useful in the invention may be delivered in the form of anti-cancer cocktails. An anti-cancer cocktail is a mixture of any one of the compounds useful with this invention with another anti-cancer agent such as an anti-cancer drug, a cytokine, and/or supplementary potentiating agent(s). The use of cocktails in the treatment of cancer is routine. In this embodiment, a common administration vehicle (e.g., pill, tablet, implant, injectable solution, etc.) would contain both the conjugate useful in this invention and the anti-cancer drug and/or supplementary potentiating agent.

Anti-cancer agents include, but are not limited to, the following compounds and classes of compounds:

Antineoplastic agents such as: Acivicin; Aclarubicin; Acodazole Hydrochloride; Acronine; Adozelesin; Adriamycin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; DACA (N-[2-(Dimethyl-amino)ethyl]acridine-4-carboxamide); Dactinomycin; Daunorubicin Hydrochloride; Daunomycin; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflornithine

Hydrochloride; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine; Fludarabine Phosphate; Fluorouracil; 5-FdUMP; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine; Interferon Alfa-2a; Interferon Alfa-2b; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta- I a; Interferon Gamma- I b; Iproplatin; Irinotecan Hydrochloride; Lanreotide Acetate; Letrozole; Leuprolide Acetate; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safingol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Thymitaq; Tiazofurin; Tirapazamine; Tomudex; TOP-53; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine; Vinblastine Sulfate; Vincristine; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride; 2-Chlorodeoxyadenosine; 2'-Deoxyformycin; 9-aminocamptothecin; raltitrexed; N-propargyl-5,8-dideazafolic acid; 2-chloro-2'-arabino-fluoro-2'-deoxyadenosine; 2-chloro-2'-deoxyadenosine; anisomycin; trichostatin A; hPRL-G129R; CEP-751; linomide; sulfur mustard; nitrogen mustard (mechlor ethamine); cyclophosphamide; melphalan; chlorambucil; ifosfamide; busulfan; N-methyl-N-nitrosourea (MNU); N, N'-Bis(2-chloroethyl)-N-nitrosourea (BCNU); N-(2-chloroethyl)-N'-

cyclohexyl-N-nitrosourea (CCNU); N-(2-chloroethyl)-N'-(trans-4-methylcyclohexyl-N-nitrosourea (MeCCNU); N-(2-chloroethyl)-N'-(diethyl)ethylphosphonate-N-nitrosourea (fotemustine); streptozotocin; diacarbazine (DTIC); mitozolomide; temozolomide; thiotepa; mitomycin C; AZQ; adozelesin; Cisplatin; Carboplatin; Ormaplatin; Oxaliplatin; C1-973; DWA 2114R; JM216; JM335; Bis (platinum); tomudex; azacitidine; cytarabine; gemcitabine; 6-Mercaptopurine; 6-Thioguanine; Hypoxanthine; teniposide

9-amino camptothecin; Topotecan; CPT-11; Doxorubicin; Daunomycin; Epirubicin; darubicin; mitoxantrone; losoxantrone; Dactinomycin (Actinomycin D); amsacrine; pyrazoloacridine; all-trans retinol; 14-hydroxy-retro-retinol; all-trans retinoic acid; N-(4-Hydroxyphenyl) retinamide; 13-cis retinoic acid; 3-Methyl TTNEB; 9-cis retinoic acid; fludarabine (2-F-ara-AMP); 2-chlorodeoxyadenosine (2-Cda).

Other anti-neoplastic compounds include: 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; amsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bleomycin A_2; bleomycin B_2; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives (e.g., 10-hydroxy- camptothecin); canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; 2'deoxycoformycin (DCF); deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-;

dioxamycin; diphenyl spiromustine; discodermolide; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocarmycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epothilones (A, R = H; B, R = Me); epithilones; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide; etoposide 4'-phosphate (etopofos); exemestane; fadrozole; fazarabine; fenretinide; filgrastim; finasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; homoharringtonine (HHT); hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide + estrogen + progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mithracin; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A + myobacterium cell wall sk; mopidamol; multiple drug resistance gene inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone + pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin;

pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; podophyllotoxin; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfinosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer.

Antiproliferative agent: Piritrexim Isothionate.

Antiprostatic hypertrophy: Sitogluside.

Benign prostatic hyperplasia therapy agent: Tamsulosin Hydrochloride.

Prostate growth inhibitor: Pentomone.

Radioactive agents: Fibrinogen I 125; Fludeoxyglucose F 18; Fluorodopa F 18; Insulin I 125; Insulin I 131; Iobenguane I 123; Iodipamide Sodium I 131; Iodoantipyrine I 131; Iodocholesterol I 131; Iodohippurate Sodium I 123; Iodohippurate Sodium I 125; Iodohippurate Sodium I 131; Iodopyracet I 125; Iodopyracet I 131; Iofetamine Hydrochloride I 123; Iomethin I 125; Iomethin I 131; Iothalamate Sodium I 125; Iothalamate Sodium I 131; Iotyrosine I 131; Liothyronine I 125; Liothyronine I 131; Merisoprol Acetate Hg 197; Merisoprol Acetate Hg 203; Merisoprol Hg 197; Selenomethionine Se 75; Technetium Tc 99m Antimony Trisulfide Colloid; Technetium Tc 99m Bicisate; Technetium Tc 99m Disofenin; Technetium Tc 99m Etidronate; Technetium Tc 99m Exametazime; Technetium Tc 99m Furifosmin; Technetium Tc 99m Gluceptate; Technetium Tc 99m Lidofenin; Technetium Tc 99m Mebrofenin; Technetium Tc 99m Medronate; Technetium Tc 99m Medronate Disodium; Technetium Tc 99m Mertiatide; Technetium Tc 99m Oxidronate; Technetium Tc 99m Pentetate; Technetium Tc 99m Pentetate Calcium Trisodium; Technetium Tc 99m Sestamibi; Technetium Tc 99m Siboroxime; Technetium Tc 99m Succimer; Technetium Tc 99m Sulfur Colloid; Technetium Tc 99m Teboroxime; Technetium Tc 99m Tetrofosmin; Technetium Tc 99m Tiatide; Thyroxine I 125; Thyroxine I 131; Tolpovidone I 131; Triolein I 125; Triolein I 131.

Anti-cancer Supplementary Potentiating Agents: Tricyclic anti-depressant drugs (e.g., imipramine, desipramine, amitryptyline, clomipramine, trimipramine, doxepin, nortriptyline, protriptyline, amoxapine and maprotiline); non-tricyclic anti-depressant drugs (e.g., sertraline, trazodone and citalopram); Ca^{++} antagonists (e.g., verapamil, nifedipine, nitrendipine and caroverine); Calmodulin inhibitors (e.g., prenylamine, trifluoroperazine and clomipramine); Amphotericin B; Triparanol analogues (e.g., tamoxifen); antiarrhythmic drugs (e.g., quinidine); antihypertensive drugs (e.g., reserpine); Thiol depleters (e.g., buthionine and sulfoximine) and Multiple Drug Resistance reducing agents such as Cremaphor EL. The compounds of the invention also can be administered with cytokines such as granulocyte colony stimulating factor.

Preferred anticancer agents used in anti-cancer coctails (e.g., in combination with the agents of the invention) include (some with their MTDs shown in parentheses): gemcitabine (1000 mg/m^2); methotrexate (15 gm/m^2 i.v.+ leuco. <500 mg/m^2 i.v. w/o leuco); 5-FU (500 mg/m^2/day x 5days); FUDR (100 mg/kg x 5 in mice, 0.6 mg/kg/day in human i.a.); FdUMP; Hydroxyurea (35 mg/kg/d in man); Docetaxel (60-100 mg/m^2); discodermolide; epothilones; vincristine (1.4 mg/m^2); vinblastine (escalating: 3.3 - 11.1 mg/m^2, or rarely to 18.5 mg/m^2); vinorelbine (30 mg/m^2/wk); meta-pac; irinotecan (50-150 mg/m^2, 1 x /wk depending on

patient response); SN-38 (~100 times more potent than Irinotecan); 10-OH campto; topotecan (1.5 mg/m^2/day in humans, 1 x iv LD10mice=75 mg/m^2); etoposide (100 mg/m^2 in man); adriamycin; flavopiridol; Cis-Pt (100mg/m^2 in man); carbo-Pt (360 mg/m^2 in man); bleomycin (20 mg/m^2); mitomycin C (20 mg/m^2); mithramycin (30 μg/kg); capecitabine (2.5 g/m^2 orally); cytarabine (100 mg/m^2/day); 2-Cl-2'deoxyadenosine; Fludarabine-PO_4 (25 mg/m^2/day, x 5days); mitoxantrone (12-14 mg/m^2); mitozolomide (>400 mg/m^2); Pentostatin; Tomudex.The compounds of the invention, when used alone or in cocktails, are administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters discussed below; but, in any event, is that amount which establishes a level of the drug(s) in the area of the tumor which is effective in inhibiting the tumor growth.

When administered, the formulations of the invention are applied in pharmaceutically acceptable amounts and in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluene sulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, and benzene sulfonic. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: acetic acid and a salt (1-2% W/V); citric acid and a salt (1-3% W/V); boric acid and a salt (0.5-2.5% W/V); and phosphoric acid and a salt (0.8-2% W/V).

Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V).

The active compounds of the present invention may be a pharmaceutical composition having a therapeutically effective amount of a conjugate of the invention optionally included in a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid filler, dilutants or encapsulating substances which are suitable for administration to a human or other animal. The term

"carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions are capable of being commingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy.

Compositions suitable for parenteral administration conveniently comprise a sterile preparation of the conjugates of the invention. This preparation may be formulated according to known methods. Formulations for Taxol and other taxanes can be found in Chapter 9 of Taxol: Science and Applications, CRC Press, Inc., 2000 Corporate Boulevard, N.W., Boca Raton, FL 33431. In general, Taxol has been formulated as a 6 mg/ml cremophor EL (polyoxyethylated castor oil)/ethanol mixture, which is diluted to final volume with normal saline or 5% dextrose. A 15mg/ml solution of taxotere has been formulated in polysorbate 80 (polyoxyethylene sorbitanmonooleate)/ethanol mixture, diluted with 5% dextrose.

The sterile preparation thus may be a sterile solution or suspension in a non-toxic parenterally-acceptable diluent or solvent. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono ordi-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables. Carrier formulations suitable for oral, subcutaneous, intravenous, intramuscular, etc. can be found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA.

The invention is used in connection with treating subjects having, suspected of having, developing or suspected of developing cancer. A subject as used herein means humans, primates, horses, cows, pigs, sheep, goats, dogs, cats and rodents.

The conjugates of the invention are administered in effective amounts. An effective amount means that amount necessary to delay the onset of, inhibit the progression of or halt altogether the onset or progression of the particular condition being treated. In general, an effective amount will be that amount necessary to inhibit mammalian cancer cell proliferation *in-situ*. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Generally, daily oral doses of active compounds will be from about 0.01 mg/kg per day to 1000 mg/kg per day. It is expected that IV doses in the range of about 1 to 1000 mg/m^2 per day will be effective. In the event that the response in a subject is insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Continuous IV dosing over, for example 24 hours or multiple doses per day are contemplated to achieve appropriate systemic levels of compounds.

A variety of administration routes are available. The particular mode selected will depend of course, upon the particular drug selected, the severity of the disease state being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the conjugates of the invention into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the active compounds of the invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel

release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

A long-term sustained release implant also may be used. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of the release systems described above. Such implants can be particularly useful in treating solid tumors by placing the implant near or directly within the tumor, thereby affecting localized, high-doses of the compounds of the invention.

The invention will be more fully understood by reference to the following examples. These examples, however, are merely intended to illustrate the embodiments of the invention and are not to be construed to limit the scope of the invention.

Examples

Example 1: Synthesis of Fatty Acid - N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) conjugates

Preparation of types 1-12 analogs, described below, refers specifically to the preparation of any of the foregoing conjugates of the invention except those where the Y group is attached to the Nitrogen next to the pyridin-4-yl group, as in conjugate 14 (or the Y_{12} group in conjugate 12).

Type 1 analogs (i.e., those containing the $-O_2CR$ subgroup), are prepared by reaction of the appropriate hydroxy-group-substituted parent drug with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 2 analogs (i.e., those containing the -NHCOR subgroup), are prepared by reaction of the appropriate amino-group-substituted parent drug with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 3 analogs (i.e., those containing the $-(CH_2)_nO_2CR$ subgroup) are prepared by reaction of the appropriate ω-hydroxy alkyl-group substituted parent drug with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 4 analogs (i.e., those containing the $-(CH_2)_nNHCOR$ subgroup) are prepared by reaction of the appropriate ω-amino alkyl-group substituted parent drug with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or

4-pyrrolidinopyridine. Type 5 analogs (i.e., those containing the $-O_2C(CH_2)_nO_2CR$ subgroup) are formed by reaction of the appropriate hydroxy-group-substituted parent drug with an ω-benzyloxy-$(CH_2)_nCO_2H$ in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine followed by hydrogenolytic removal of the benzyl protecting group and subsequent reaction of the deprotected intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 6 analogs (i.e., those containing the $-O_2C(CH_2)_nNHCOR$ subgroup) are formed by reaction of the appropriate hydroxy-group-substituted parent drug with an ω-$PhCH_2OCONH$-$(CH_2)_nCO_2H$ in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine followed by hydrogenolytic removal of the benzyloxycarbonyl protecting group and subsequent reaction of the deprotected intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 7 analogs (i.e., those containing the $-O(CH_2)_nO_2CR$ subgroup) are prepared by reaction of the appropriate hydroxy-group-substituted parent drug with a 1-benzyloxy-ω-iodo-*n*-alkane in the presence of base followed by hydrogenolytic removal of the benzyl protecting group and subsequent reaction of the deprotected intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 8 analogs (i.e., those containing the $-O(CH_2)_nNHCOR$ subgroup) are prepared by reaction of the appropriate hydroxy-group-substituted parent drug with a 1-azido-ω-iodo-*n*-alkane in the presence of base followed by hydrogenation and subsequent reaction of the primary amine intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 9 analogs (i.e., those containing the $-NHCO(CH_2)_nO_2CR$ subgroup) are prepared by reaction of the appropriate amino-group-substituted parent drug with an ω-benzyloxy-$(CH_2)_nCO_2H$ in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine followed by hydrogenolytic removal of the benzyl protecting group and subsequent reaction of the deprotected intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 10 analogs (i.e., those containing the $-NHCO(CH_2)_nNHCOR$ subgroup) are prepared by reaction of the appropriate amino-group-substituted parent drug with an ω-$PhCH_2OCONH$-$(CH_2)_nCO_2H$ in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent

and 4-dimethylaminopyridine or 4-pyrrolidinopyridine followed by hydrogenolytic removal of the benzyloxycarbonyl protecting group and subsequent reaction of the deprotected intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 11 analogs (i.e., those containing the $-NH(CH_2)_nO_2CR$ subgroup) are prepared by reaction of the appropriate amino-group-substituted parent drug and a 1-benzyloxy-ω-iodo-*n*-alkane followed by hydrogenolytic removal of the benzyl protecting group and subsequent reaction of the deprotected intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 12 analogs (i.e., those containing the $-NH(CH_2)_nNHCOR$ subgroup) are prepared by reaction of the appropriate amino-groups-substituted parent drug with a 1-azido-ω-iodo-*n*-alkane followed by hydrogenation and subsequent reaction of the primary amine intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Those skilled in the art will recognize other synthetic pathways to these fatty acid conjugates.

Preparation of types 13-17 analogs, described below, refers to the preparation of any of the foregoing conjugates of the invention where the Y group is attached specifically to the Nitrogen next to the pyridin-4-yl group, as in conjugate 14 (or the Y_{12} group in conjugate 12).

Type 13 analogs (i.e., those containing the -COR subgroup) are prepared by sequential reaction of the parent drug with sodium hydride or another base and a fatty acid-derived acid chloride. Type 14 analogs (i.e., those containing the $-(CH_2)_nO_2CR$ subgroup) are prepared by sequential reaction of the parent drug with sodium hydride or another base and a 1-benzyloxy-ω-iodo-*n*-alkane followed by hydrogenolytic removal of the benzyl protecting group and subsequent reaction of the deprotected intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 15 analogs (i.e., those containing the $-(CH_2)_nNHCOR$ subgroup) are prepared by sequential reaction of the parent drug with sodium hydride or another base and an 1-azido-ω-*n*-alkane followed by hydrogenation and subsequent reaction of the primary amine intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 16 analogs (i.e., those containing the $-CO(CH_2)_nO_2CR$ subgroup) are prepared by sequential reaction of the parent drug with sodium hydride or another base and an ω-benzyloxy-$(CH_2)_nCO_2H$-derived acid chloride followed by hydrogenolytic removal of the benzyl protecting group and subsequent reaction of the

deprotected intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Type 17 analogs (i.e., those containing the $-CO(CH_2)_nNHCOR$ subgroup) are prepared by sequential reaction of the parent drug with sodium hydride or another base and an ω-azido-$(CH_2)_nCO_2H$-derived acid chloride followed by hydrogenation and subsequent reaction of the primary amine intermediate with a fatty acid in the presence of dicyclohexylcarbodiimide or other carboxyl-activating agent and 4-dimethylaminopyridine or 4-pyrrolidinopyridine. Those skilled in the art will recognize other synthetic pathways to these fatty acid conjugates.

Example 2: The Effects of Taxoprexin and Paclitaxel Against M 109 Lung Carcinoma in Mice

Syngeneic mice were injected with mouse lung tumor line M (Madison) 109 subcutaneously in the flank. Five days after tumor implantation, one day later than in the last example, when the tumors had grown ten-fold larger to 300 mg, taxoprexin (OD=120mg/kg/day x 5 days) or paclitaxel (OD=20mg/kg/day x 5 days) were injected as a bolus through the tail vein on each of five successive days. Both drugs were dissolved in 10% cremophor EL/10% ethanol/80% saline. Tumor volume was estimated from tumor width and length. Paclitaxel retarded tumor growth for about four days (LCK=1.0). In contrast, taxoprexin completely eliminated all measurable tumors in seven out of eight mice (C/T=7/8) at 120 mg/kg/day x 5 days, and in four out of seven mice at 80 mg/kg/day x 5 days. Histological examination of the tissue where the tumors had showed no tumor cells, only scar tissue. These data show that taxoprexin is curative in this model.

Example 3: Response of Human NCI-H522 Lung Tumor to Treatment with Taxoprexin and Paclitaxel in Mice

The Southern Research Institute studied the anti-tumor activity of taxoprexin against human NCI-H522 lung tumor growing in nude mice. The tumors were implanted subcutaneously. Tumor mass was determined by calculation from tumor length and width. The drugs were dissolved in 12.5% cremophor EL/12.5% ethanol/75% saline and delivered i.v. into the tail vein, once a day for 5 days, from day 15 to 19 after tumor implantation. The results show that taxoprexin at 50 mg/kg/day x 5 days and paclitaxel at 20 mg/kg/day x 5 days eliminated all measurable tumors in 10/10 mice.

Example 4: The Pharmacokinetic Parameters of Taxoprexin and Paclitaxel

Rats were dosed for three minutes with 6.8mg/kg of taxoprexin through the tail vein. The drug was dissolved in 10% cremaphor EL/10% ethanol/80% saline. The serum concentrations of both taxoprexin and paclitaxel were measured in a reverse phase HPLC

assay. Pharmacokinetic parameters were calculated from these data. Taxoprexin has ~ 100 fold lower clearance rate and volume of distribution (see Table 1).

Table 1.

Taxoprexin® Pharmacokinetic Parameters in Rats

Drug	Clearance	Plasma $t_{1/2}$ (hr) (n=3)	Volume of Distribution
Paclitaxel	28.2 ml/min/kg	4.8±2.6	4.3 L/kg
Taxoprexin®	0.3 ml/min/kg	4.8±0.1	0.058 L/kg

Example 5: Plasma Concentration of Taxoprexin and Paclitaxel in Rats Following I.V. Administrations of Taxoprexin

Rats were given a 3 minute intravenous infusion of taxoprexin through the tail vein at 0 time. The drug was dissolved in 10% cremophor EL/10% ethanol/80% saline. The dose was 6.8 mg/kg. The concentrations in serum of both paclitaxel and taxoprexin as a function of time were measured in a reverse phase HPLC assay (see Table 2).

Table 2.

Paclitaxel and *Taxoprexin*® plasma concentration (ng/ml) following administration of *Taxoprexin*® in Rats

Time (hr)	Paclitaxel	*Taxoprexin*®
0	200	100,000
1	100	95,000
2	70	90,000
5	40	70,000
24	10	40,000

Example 6: Plasma and Tumor Concentrations of Paclitaxel Derived from an I.V. Dose of 50 mg/kg of Taxoprexin to Mice Bearing M 109 or M 5076 Tumors

Mice with tumors derived from M109 or M5076 were given a bolus does of taxoprexin through the tail vein at 0 time. The drug was dissolved in 10% cremophor EL/10% ethanol/80% saline. Mice were sacrificed and tumors immediately excised as a function of time after injecting the drug. Tumor tissue was homogenized and paclitaxel extracted. The concentration of paclitaxel was measured in a reverse phase HPLC assay. Blood was collected at the same time intervals and the amount of paclitaxel determined. The results show that after 24 hours the concentration of paclitaxel derived from taxoprexin is about 3 μM, 40 times higher than the plasma concentration, 70 nM. Each data point is the mean of three measurements (n=3). NOTE: Paclitaxel has a $t_{1/2}$ of <8 hours in the same tumor system.

Example 7: Dose Comparisons (MTD and Est LD_{40}) of Taxoprexin and Paclitaxel in Various Species Except Humans

Dose comparisons for paclitaxel and taxoprexin were made in mice, rats and dogs. The maximum tolerated dose (MTD) for mice, rats and dogs were about 4-5 times higher for taxoprexin than for paclitaxel on a mg/kg basis, or 3-3.5 times higher on a molar paclitaxel equivalent basis. Dose limiting toxicity for rats and dogs is due to decreases in platelets, neutrophils and lymphocytes. Taxoprexin is less toxic to mice, rats and dogs than is paclitaxel(see Table 3).

Table 3.

Dose Comparisons: Paclitaxel vs. *Taxoprexin*® in various species

Species	Dose (mg/kg)*		Dose ratio: *Taxoprexin*®/Paclitaxel	
	Taxoprexin®	Paclitaxel	Based on Weight	Based on Taxane Molarity**
Mouse	MTD = 100 x 5 = 500	MTD = 20 x 5 =100	5	3.6
Rat	Est LD_{40} = 420	LD_{40} = 85	5	3.6
Dog	MTD = 80	Est MTD = 20	4	2.9
		Average	*4.7*	*3.4*

* MTD is Maximum Tolerated Dose

**MW of *Taxoprexin*® = 1164; MW of Paclitaxel = 854; MW ratio = 0.73

The foregoing data establish, surprisingly, safety implications of dose and pharmacokinetic advantages of taxoprexin. The higher MTD of taxoprexin compared to paclitaxel is believed to lead to greater safety of taxoprexin with much greater efficacy. The smaller volume of distribution for taxoprexin is believed to lead to less damage by taxoprexin in peripheral tissues including, but not limited to, nerves, hair follicles, GI cells, etc. The longer residence time of taxoprexin in tumors is believed to lead to fewer required dosing cycles for optimum therapeutic efficacy, which is believed to lead to decreased systemic toxicity. Taxoprexin thus appears to have a 100 fold lower clearance rate and volume of distribution than paclitaxel. In addition, levels of paclitaxel in tumors treated with taxoprexin remain stable for 24 hours, whereas such levels in tumors treated with paclitaxel have stable levels for less than 8 hours. Finally, taxoprexin was shown to cure 3/8 mice of the human HCT colon tumor, while paclitaxel cured 0/8. HCT is a paclitaxel resistant tumor.

Other aspects of the invention will be clear to the skilled artisan and need not be repeated here. All patents, published patent applications and literature cited herein are incorporated by reference in their entirety. We claim:

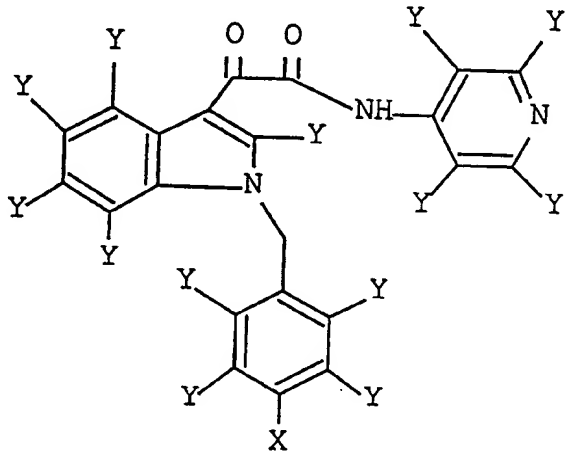
Claims

1. A compound, comprising:

a covalent conjugate of N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) and a fatty acid having 12-26 carbons.

2. The compound of claim 1, wherein the N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) is N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide).

3. The compound of claim 1, wherein the covalent conjugate is

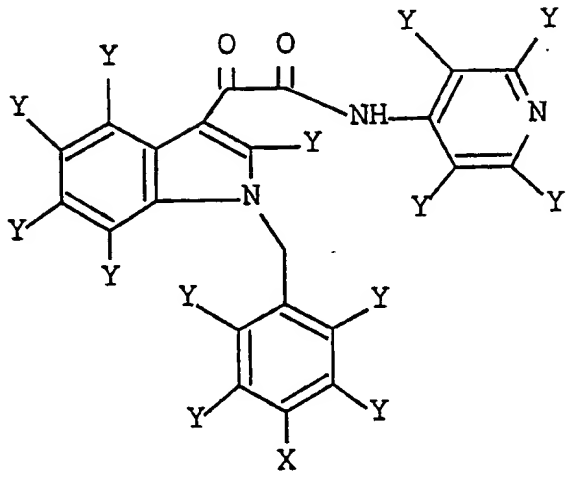


wherein X is F, Cl, Br, I, or Y,

wherein Y is selected from the group consisting of -H, $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22, and

wherein at least one Y is not H and is selected from the group consisting of $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $-NH(CH_2)_nO_2CR$, and $-NH(CH_2)_nNHCOR$, wherein n=1-22, the remainining Y groups are unsubstituted and are H.

4. The compound of claim 1, wherein the covalent conjugate is

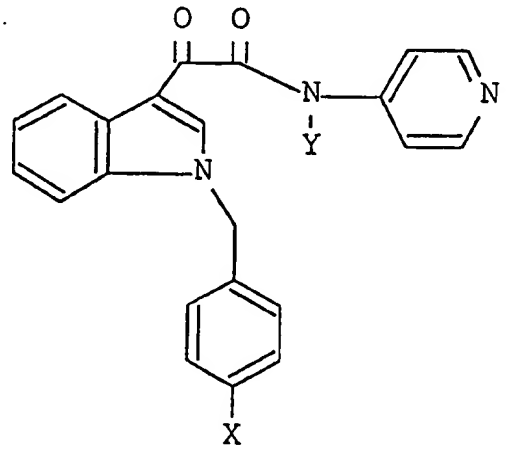


wherein X is F, Cl, Br, I, or Y,

wherein Y is selected from the group consisting of -H, $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-O_2C(CH_2)_nO_2CR$, $-O_2C(CH_2)_nNHCOR$, $-O(CH_2)_nO_2CR$, $-O(CH_2)_nNHCOR$, $-NHCO(CH_2)_nO_2CR$, $-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22, and

wherein at least two Y groups are not H and are selected from the group consisting of $-O_2CR$,-NHCOR,$-(CH_2)_nO_2CR$,$-(CH_2)_nNHCOR$,$-O_2C(CH_2)_nO_2CR$,$-O_2C(CH_2)_nNHCOR$,$-O(CH_2)_nO_2CR$,$-O(CH_2)_nNHCOR$,$-NHCO(CH_2)_nO_2CR$,$-NHCO(CH_2)_nNHCOR$, $NH(CH_2)_nO_2CR$, $-NH(CH_2)_nNHCOR$, wherein n=1-22, the remainining Y groups are unsubstituted and are H.

5. The compound of claim 1, wherein the covalent conjugate is



wherein X is selected from the group consisting of H, F, Cl, Br, I, $-O_2CR$, -NHCOR, $-(CH_2)_nO_2CR$,$-(CH_2)_nNHCOR$,$-O_2C(CH_2)_nO_2CR$,$-O_2C(CH_2)_nNHCOR$,$-O(CH_2)_nO_2CR$,$-O(CH_2)_nNHCOR$,$-NHCO(CH_2)_nO_2CR$,$-NHCO(CH_2)_nNHCOR$,$-NH(CH_2)_nO_2CR$, and $-NH(CH_2)_nNHCOR$, wherein n=1-22, and

wherein Y is selected from the group consisting of -COR, $-(CH_2)_nO_2CR$, $-(CH_2)_nNHCOR$, $-CO(CH_2)_nO_2CR$, and $-CO(CH_2)_nNHCOR$, wherein n=1-22.

6. The compound of claims 1, 2, 3, 4, or 5 wherein the fatty acid is an unbranched, naturally occurring fatty acid.

7. The compound of claim 6, wherein the fatty acid has 16-22 carbons.

8. The compound of claim 7, wherein the fatty acid is docosahexaenoic acid.

9. A pharmaceutical composition comprising the compound of claim 1, 2, 3, 4, or 5 in an amount effective to treat cancer, and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition comprising the compound of claim 6 in an amount effective to treat cancer, and a pharmaceutically acceptable carrier.

11. A pharmaceutical composition comprising the compound of claim 7 in an amount effective to treat cancer, and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition comprising the compound of claim 8 in an amount effective to treat cancer, and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 9, further comprising an anti-cancer agent other than the covalent conjugate.

14. The pharmaceutical composition of claim 13, wherein the anti-cancer agent is selected from the group consisting of Aminoglutethimide; Asparaginase; Bleomycin; L-Buthiamine Sulfoxide; Busulfan; Camptothecin; Carboplatin; Carmustine (BCNU); Chlorambucil; Cisplatin (cis-DDP); Cyclophosphamide; Cytarabine HCl; Dacarbazine; Dactinomycin; Daunorubicin HCl; Doxorubicin HCl; Edatrexate; Estramustine phosphate sodium; Etoposide

(V16-213); Floxuridine; Fluorouracil (5-FU); Flutamide; Gallium Nitrite; Hydroxyurea (hydroxycarbamide); Idarubicin; Ifosfamide; Interferon-α-2a, -α2b; Leuprolide acetate (LHRH-releasing factor analogue); Lomustine (CCNU); Mechlorethamine HCI (nitrogen mustard); Megestrol; melphalan; Mercaptopurine; Methotrexate (MTX); Mitomycin; Mitotane (o.p'-DDD); Mitoxantrone HCI; Octreotide; Plicamycin; Prednisone; Procarbazine HCI; Streptozocin; Tamoxifen citrate; Taxanes; Taxoids; Thioguanine; Thiotepa; Tiasofuran; Topotecan; Vinblastine sulfate; Vincristine sulfate; Amsacrine (m-AMSA); Azacitidine; Hexamethylmelamine (HMM); Interleukin 2; Mitoguazone (methyl-GAG); Methyl glyoxal bis-guanylhydrazone (MGBG); Paclitaxel; Pentostatin; Semustine (methyl-CCNU); Taxol; Taxotere; Tamoxifen; and Teniposide (VM-26).

15. A kit comprising a package housing a container containing the compound of claims 1, 2, 3, 4, or 5, and also housing instructions for administering to a cancer victim the covalent conjugate.

16. A kit comprising a package housing:
a first container containing the covalent conjugate of claim 1, 2, 3, 4, or 5, and
a second container containing an anti-cancer agent other that the covalent conjugate.

17. A method for treating a subject having or suspected of having cancer, comprising: administering to a subject in need of such treatment an amount of a covalent conjugate of N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amid) and a fatty acid having 12-26 carbons in an amount effective to treat cancer.

18. The method of claim 17, wherein the N-(pyridin-4-yl)-(1-(4-halobenzyl)-indol-3-yl)-glyoxyl-amide) is N-(pyridin-4-yl)-(1-(4-chlorobenzyl)-indol-3-yl)-glyoxyl-amide).

19. The method of claim 17, wherein the covalent conjugate comprises the pharmaceutical preparation of claim 9.

20. The method of claim 17, wherein the covalent conjugate comprises the pharmaceutical preparation of claim 10.

21. The method of claim 17, wherein the covalent conjugate comprises the pharmaceutical preparation of claim 11.

22. The method of claim 17, wherein the covalent conjugate comprises the pharmaceutical preparation of claim 12.

23. The method of claim 19, further comprising administering to the subject an anti-cancer agent other than the covalent conjugate.

24. The method of claim 23, wherein the anti-cancer agent is selected from the group consisting of Aminoglutethimide; Asparaginase; Bleomycin; L-Buthiamine Sulfoxide; Busulfan; Camptothecin; Carboplatin; Carmustine (BCNU); Chlorambucil; Cisplatin (cis-DDP); Cyclophosphamide; Cytarabine HCl; Dacarbazine; Dactinomycin; Daunorubicin HCl; Doxorubicin HCl; Edatrexate; Estramustine phosphate sodium; Etoposide (V16-213); Floxuridine; Fluorouracil (5-FU); Flutamide; Gallium Nitrite; Hydroxyurea (hydroxycarbamide); Idarubicin; Ifosfamide; Interferon Alfa-2a, Alfa 2b; Leuprolide acetate (LHRH-releasing factor analogue); Lomustine (CCNU); Mechlorethamine HCl (nitrogen mustard); Megestrol; melphalan; Mercaptopurine; Methotrexate (MTX); Mitomycin; Mitotane (o.p'-DDD); Mitoxantrone HCl; Octreotide; Plicamycin; Prednisone; Procarbazine HCl; Streptozocin; Tamoxifen citrate; Taxanes; Taxoids; Thioguanine; Thiotepa; Tiasofuran; Topotecan; Vinblastine sulfate; Vincristine sulfate; Amsacrine (m-AMSA); Azacitidine; Hexamethylmelamine (HMM); Interleukin 2; Mitoguazone (methyl-GAG); Methyl glyoxal bis-guanylhydrazone (MGBG); Paclitaxel; Pentostatin; Semustine (methyl-CCNU); Taxol; Taxotere; and Teniposide (VM-26).

25. A fatty acid-anti cancer compound conjugate pharmaceutical composition for administration to a subject, comprising at least one fatty acid-anti cancer compound conjugate in a container for administration to a subject, wherein the amount of the fatty acid-anti cancer compound in the container is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anti cancer compound wherein the conjugate is a compound of claim 1.

26. The fatty acid-anti cancer compound conjugate composition of claim 25, wherein the amount in the container is at least about 20%, at least about 30%, at least about 40%, at least

about 50%, at least about 75%, or at least about 100% greater than the MTD for the unconjugated at least one anti cancer compound.

27. The fatty acid-anti cancer compound conjugate composition of claim 25, wherein the amount in the container is at least about 200% greater than the MTD for the unconjugated at least one anti cancer compound.

28. The fatty acid-anti cancer compound conjugate composition of claim 25, wherein the amount in the container is at least about 300% greater than the MTD for the unconjugated at least one anti cancer compound.

29. The fatty acid-anti cancer compound conjugate composition of claim 25, wherein the amount in the container is at least about 400% greater than the MTD for the unconjugated at least one anti cancer compound.

30. The fatty acid-anti cancer compound conjugate composition of claim 25, wherein the container is a container for intravenous administration.

31. The fatty acid-anti cancer compound conjugate composition of claim 25, wherein the fatty acid is a C16-22 unbranched, naturally occurring fatty acid.

32. The fatty acid-anti cancer compound conjugate composition of claim 25, wherein the fatty acid is docosahexaenoic acid

33. A method for treating a subject having an abnormal mammalian cell proliferative disorder, comprising administering to the subject a fatty acid-anti cancer compound conjugate composition in an amount which is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anti cancer compound, wherein the conjugate is a compound of claim 1.

34. The method of claim 33, wherein the amount of the fatty acid-anti cancer compound conjugate composition administered is at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 75%, or at least about 100% greater than the MTD for the unconjugated at least one anti cancer compound.

35. The method of claim 33, wherein the amount of the fatty acid-anti cancer compound conjugate composition administered is at least about 200% greater than the MTD for the unconjugated at least one anti cancer compound.

36. The method of claim 33, wherein the amount of the fatty acid-anti cancer compound conjugate composition administered is at least about 300% greater than the MTD for the unconjugated at least one anti cancer compound.

37. The method of claim 33, wherein the amount of the fatty acid-anti cancer compound conjugate composition administered is at least about 400% greater than the MTD for the unconjugated at least one anti cancer compound.

38. The method of claim 33, wherein the fatty acid is a C16-C22 unbranched, naturally occurring fatty acid.

39. The method of claim 33, wherein the fatty acid is docosahexaenoic acid.

40. A kit for administration of a fatty acid-anti cancer compound conjugate composition to a subject, comprising

a container containing at least one fatty acid-anti cancer compound conjugate, and

instructions for administering the at least one fatty acid-anti cancer compound conjugate to subject in need of such treatment in an amount which is at least about 10% greater than the maximum tolerated dose (MTD) for the unconjugated at least one anti cancer compound, wherein the conjugate is a compound of claim 1.

41. The kit of claim 40, wherein the amount of the at least one fatty acid-anti cancer compound conjugate is at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 75%, or at least about 100% greater than the MTD for the unconjugated at least one anti cancer compound.

42. The kit of claim 40, wherein the amount of the at least one fatty acid-anti cancer compound conjugate is at least about 200% greater than the MTD for the unconjugated at least one anti cancer compound.

43. The kit of claim 40, wherein the amount of the at least one fatty acid-anti cancer compound conjugate is at least about 300% greater than the MTD for the unconjugated at least one anti cancer compound.

44. The kit of claim 40, wherein the amount of the at least one fatty acid-anti cancer compound conjugate is at least about 400% greater than the MTD for the unconjugated at least one anti cancer compound.

45. The kit of claim 40, wherein the fatty acid is a C16-C22 unbranched, naturally occurring fatty acid.

46. The kit of claim 40, wherein the fatty acid is docosohexaenoic acid.

47. A method for increasing the therapeutic index of anti cancer compounds in a subject, comprising

conjugating a fatty acid to a compound from claim 1 to form a fatty acid-anti cancer compound conjugate; and

administering the fatty acid-anti cancer compound conjugate to the subject, whereby the therapeutic index of the compound of claim 1 is improved relative to non-conjugated formulations of the compound of claim 1.

48. The method of claim 47, wherein the fatty acid is a C16-C22 unbranched, naturally occurring fatty acid.

49. The method of claim 47, wherein the fatty acid is docosohexaenoic acid.

50. The method of claim 47, wherein the subject is human.

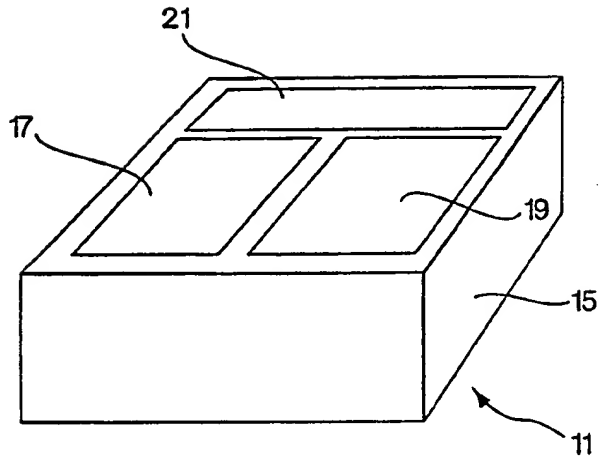


Fig. 1

INTERNATIONAL SEARCH REPORT

Ir ational Application No
PCT/US 00/12752

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 97 44026 A (NEUROMEDICA INC) 27 November 1997 (1997-11-27) abstract page 23 -page 24; claims 1-14; examples 1-3 ---	1-50
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
25 October 2000	31/10/2000

Name and mailing address of the ISA	Authorized officer
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